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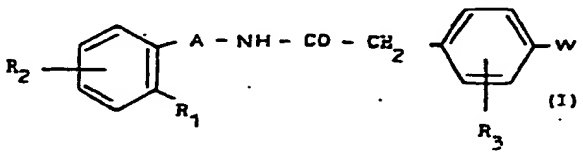
(54) Substituted phenylacetamides

(57) Compounds of general formula I



(I)

(wherein R_1 is optionally substituted polymethyleneimino or dialkylamino; A is substituted CH_2; and R_2, R_3, and W are as defined in the specification) and tautomers, optical enantiomers and salts thereof.

The new compounds have valuable pharmacological properties, particularly a hypoglycaemic effect.

Processes for the preparation of the new compound and pharmaceutical compositions containing them are described.

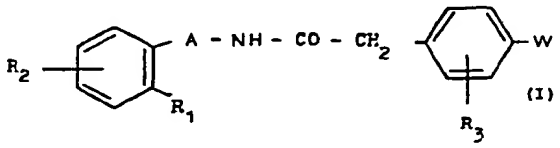
GB 2 124 220 A

SPECIFICATION

Chemical compounds

The present invention relates to new phenylacetic acid derivatives, to processes for their preparation, and to their effects on intermediate metabolism and the cardiac circulatory system.

According to one feature of the present invention, we provide compounds of general formula I



(I)

[wherein

A represents a group of formula

[wherein R_4 represents an alkyl group containing 1 to 3 carbon atoms optionally substituted by an alkoxy group containing 1 to 3 carbon atoms or by a phenyl group; an alkyl group containing 4 to 7 carbon atoms; an alkenyl group containing 3 to 5 carbon atoms; a cyano or alkyleneiminocarbonyl group containing 4 to 6 carbon atoms in the alkylene moiety; an aminocarbonyl group optionally mono- or disubstituted by alkyl or phenylalkyl groups each having 1 to 3 carbon atoms in the alkyl moiety (the substitutents in the case of disubstitution being the same or different); an aryl group containing 6 or 10 carbon atoms optionally mono- or disubstituted by halogen atoms, or by alkyl, hydroxy, alkoxy, phenylalkoxy, alkylsulphenyl, alkylsulphinyl and/or alkylsulphonyl groups, the substituents in the case of disubstitution being the same or different and each alkyl moiety containing 1 to 3 carbon atoms; or a heteroaryl group containing 4, 5, 8 or 9 carbon atoms and 1 or 2 nitrogen atoms;

R_5 and R_6, which may be the same or different, represent hydrogen atoms or alkyl groups containing 1 to 5 carbon atoms, or R_5 and R_6 together with the carbon atom between them represent a phenylalkylidene group containing 1 to 4 carbon atoms in the alkylidene moiety],

R_1 represents an unbranched alkyleneimino group containing 4 to 9 carbon atoms optionally mono- or disubstituted by alkyl groups containing 1 to 3 carbon atoms (which in the case of disubstitution may be the same or different); or a dialkylamino group containing 1 to 5 carbon atoms in each alkyl component,

R_2 represents a hydrogen, fluorine, chlorine, bromine or iodine atom, or a hydroxy, trifluoromethyl, nitro, amino, piperidino, alkyl, alkoxy, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, phenylalkoxy, alkanoyloxy, alkanoylamino, alkylamino or dialkylamino group wherein the alkyl component may contain 1 to 3 carbon atoms in each case,

R_3 represents an alkyl group containing 1 to 3 carbon atoms or a hydrogen or halogen atom, and

W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 6 carbon atoms (wherein the alkyl component may optionally be substituted by a phenyl group and optionally, at any carbon atom except the α-carbon atom, by one or two hydroxy groups or by an alkoxy, alkanoyloxy, dialkylamino, alkyleneimino or pyridinecarbonyloxy group, each alkyl component containing 1 to 3 carbon atoms and the alkyleneimino group containing 4 to 6 carbon atoms); an alkenyloxycarbonyl group containing a total of 4 to 6 carbon atoms, an alkyl group containing 1 to 3 carbon atoms; or a hydroxymethyl, formyl, cyano, aminocarbonyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, 2,2-bis-(carboxy)-ethyl, alkoxycarbonyl-methyl, 2-alkoxycarbonyl-ethyl, 2-alkoxycarbonyl-ethenyl or 2,2-bis-(alkoxycarbonyl)-ethyl group (each alkoxy group containing from 1 to 3 carbon atoms)]

and tautomers thereof and optical enantiomers thereof and salts of the aforementioned compounds.

It will be appreciated that the term "salts" as used herein includes within its scope salts formed with organic and inorganic acids and bases. Suitable acids include, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, lactic, citric, tartaric, succinic, maleic or fumaric acid. Suitable bases include, for example, sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine, triethanolamine or ethylenediamine.

For pharmaceutical use, the salts referred to above will, of course, by physiologically compatible salts, but other salts may fine use, for example in the preparation of the compounds of general formula I and their physiologically compatible salts.

The term "tautomer" as used herein refers particularly to the tautomeric ketimine form of the compounds of general formula I wherein A represents a substituted vinylidene radical, but the term is not restricted to this interpretation and covers all possible tautomeric forms of the compounds of general formula I.

The definitions given hereinbefore for the groups R_1 to R_6 and W include the following, for example:

R_1 may represent a dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, di-n-pentylamino, diisobutylamino, N-methyl-ethylamino, N-methyl-n-propylamino, N-methyl-isopropylamino, N-isopropyl-n-propylamino, N-isobutyl-n-propylamino, N-methyl-n-butylamino, N-ethyl-n-butylamino, N-ethyl-isopropylamino, N-ethyl-n-pentylamino, N-propyl-n-butylamino, pyrrolidino, piperidino, hexamethyleneimino, heptamethyleneimino, octamethyleneimino, nonamethyleneimino, methyl-pyrrolidino, dimethyl-pyrrolidino, ethyl-pyrrolidino, methyl-piperidino, ethyl-piperidino, dimethyl-piperidino, diethyl-piperidino, methyl-ethylpiperidino, n-propyl-piperidino, methyl-n-propylpiperidino, isopropylpiperidino, or di-n-propyl-piperidino group,

This print takes account of replacement documents later filed to enable the application to comply with the formal requirements of the Patents Rules 1982

R_2 may represent a hydrogen, fluorine, chlorine, bromine or iodine atom or a methyl, ethyl, n-propylisopropyl, hydroxy, methoxy, ethoxy, n-propoxy, isopropoxy, trifluoromethyl, nitro, amino, piperidino, methylmercapto, ethylmercapto, n-propylmercapto, isopropylmercapto, methylsulphinyl, ethylsulphinyl, methylsulphonyl, n-propylsulphonyl, benzyloxy, 1-phenyl-ethoxy, 2-phenyl-ethoxy, 3-phenyl-propoxy, acetoxy, propionyloxy, formylamino, acetylamino, propionylamino, methylamino, ethylamino, n-propylamino, dimethylamino, diethylamino, di-n-propylamino or methyl-ethylamino group,

R_3 may represent a hydrogen, fluorine, chlorine or bromine atom or a methyl, ethyl, n-propyl or isopropyl group,

R_4 may represent a methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, 2-methoxyethyl, 2-ethoxy-ethyl, 3-methoxy-propyl, benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenyl-n-propyl, 2-phenyl-n-propyl, 3-phenylpropyl, allyl, 3-buten-1-yl, 2-buten-1-yl, 4-penten-1-yl, cyano, aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl-n-propylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, benzylaminocarbonyl, 2-phenyl-ethylaminocarbonyl, pyrrolidinocarbonyl, piperidinocarbonyl, hexamethyleneiminocarbonyl, phenyl, naphthyl, fluorophenyl, chlorophenyl, bromophenyl, methylphenyl, ethylphenyl, isopropylphenyl, hydroxyphenyl, methoxyphenyl, ethoxyphenyl, n-propoxyphenyl, benzyloxyphenyl, 2-phenyl-ethoxy-phenyl, 3-phenylpropoxy-phenyl, methylsulphenyl-phenyl, ethylsulphenyl-phenyl, methyl-sulphinyl-phenyl, n-propylsulphinyl-phenyl, methyl-sulphonyl-phenyl, ethylsulphonyl-phenyl, isopropylsulphonyl-phenyl, methyl-naphthyl, hydroxy-naphthyl, methoxy-naphthyl, dichlorophenyl, chloro-bromo-phenyl, dimethyl-phenyl, di-isopropyl-phenyl, chloro-methyl-phenyl, dimethoxy-phenyl, methyl-methoxyphenyl, chloro-methoxy-phenyl, bromo-methoxy-phenyl, pyridyl, pyrimidyl, quinolyl, isoquinolyl or quinazolyl group,

R_5 and R_6 may represent a hydrogen atom or a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl or n-pentyl group,

R_5 and R_6 together with the carbon atoms between them may represent a benzylidene, 1-phenyl-ethylidene, 2-phenyl-ethylidene, 1-phenyl-n-propylidene, 1-phenyl-2,2-propylidene or 3-phenyl-n-propylidene group and

W may represent a hydroxymethyl, formyl, carboxy, carboxymethyl, 2-carboxy-ethyl, 2-carboxy-ethenyl, 2,2-bis (carboxy)-ethyl, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, n-pentoxycarbonyl, allyloxycarbonyl, crotyloxycarbonyl, (2-hydroxyethoxy) carbonyl, (2-hydroxy-n-propoxy) carbonyl, (1-hydroxy-2-propoxy) carbonyl, (2-methoxyethoxy) carbonyl, (2-ethoxyethoxy) carbonyl, (2-n-propoxyethoxy) carbonyl, (2-nicotinoyloxy-ethoxy) carbonyl, (2-isonicotinoyloxy-ethoxy) carbonyl, (2,3-dihydroxy-n-propoxy) carbonyl, (2-dimethylamino-ethoxy) carbonyl, (2-diethylamino-ethoxy) carbonyl, (2-piperidino-ethoxy) carbonyl, methyl, ethyl, n-propyl, isopropyl, cyano, aminocarbonyl, methoxycarbonyl-methyl, ethoxycarbonyl-methyl, n-propoxycarbonyl-methyl, 2-methoxycarbonyl-ethyl, 2-ethoxycarbonyl-ethyl, 2-isopropoxycarbonyl-ethyl, 2-methoxycarbonyl-ethenyl, 2-ethoxycarbonyl-ethenyl, 2-n-propoxycarbonyl-ethenyl, 2,2-bis-(methoxycarbonyl)-ethyl, 2,2-bis-(ethoxycarbonyl)-ethyl or 2,2-bis-(isopropoxycarbonyl)-ethyl group.

Preferred compounds of general formula I above are those wherein

A represents a group of formula

wherein R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by an alkoxy group containing 1 to 3 carbon atoms or by a phenyl group; an n-propyl group; an alkyl group containing 4 to 6 carbon atoms; an alkenyl group containing 3 to 5 carbon atoms; a cyano or aminocarbonyl group; an aryl group containing 6 or 10 carbon atoms mono- or disubstituted by halogen atoms, or by alkyl, hydroxy, alkoxy, phenylalkoxy and/or alkylsulphenyl groups, whilst the substituents may be the same or different and each alkyl component may contain from 1 to 3 carbon atoms; or a naphthyl, pyridyl, quinolyl or isoquinolyl group;

R_5 and R_6 together with the carbon atom between them represent an alkylidene group containing 3 to 9 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene moiety;

R_1 represents an unbranched alkyleneimino group containing 4 to 8 carbon atoms or a piperidino group mono- or disubstituted by alkyl groups each having 1 to 3 carbon atoms;

R_2 represents a hydrogen, fluorine, chlorine or bromine atom or a nitro, alkyl or alkoxy group each having 1 to 3 carbon atoms, or (if R_5 and R_6 are as hereinbefore defined or R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by an alkoxy group with 1 to 3 carbon atoms or by a phenyl group, an n-propyl group, an alkyl group containing 4 to 6 carbon atoms, an alkenyl group containing 3 to 5 carbon atoms, or a nitrile or aminocarbonyl group) R_2 may also represent an iodine atom or a hydroxy or amino group;

R_3 represents a hydrogen or chlorine atom; and

W represents a methyl, hydroxymethyl, formyl, cyano, carboxy, carboxymethyl, 2-carboxyl-ethyl or 2-carboxy-ethenyl group; an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms in which the alkyl component may be substituted at any carbon atom except the α-carbon atom by 1 or 2 hydroxy groups or by an alkoxy group containing 1 to 3 carbon atoms or by a pyridinecarbonyloxy group; or an alkoxycarbonyl-methyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group, wherein each alkoxy group may contain from 1 to 3 carbon atoms and

4-[N-(6-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl

esters thereof,
4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamic acid and C_{1-3} alkyl esters thereof,
3-[4-[(N-(α-phenyl-2-piperidino-benzyl)-aminocarboxylmethyl]-phenyl]-propionic acid and C_{1-3} alkyl esters thereof,
4-[N-(4-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(3-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(2-(2-methyl-piperidino)-α-phenyl-benzyl)-aminocarboxylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(2-(3-methyl-piperidino)-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethylbenzaldehyde,
4-[(1-(4-fluoro-2-piperidino-phenyl)-ethyl) aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[(1-(3-chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof, and
4-[(1-(3-methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl] benzoic acid and C_{1-3} alkyl esters thereof.

Particularly preferred are those compounds of general formula I wherein

A represents a group of formula

wherein R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by a methoxy or phenyl group; an n-propyl, cyano or aminocarbonyl group; an alkyl group containing 4 to 6 carbon atoms, an alkenyl group containing 3 to 5 carbon atoms; a phenyl group substituted by a fluorine, chlorine or bromine atom or by a methyl, hydroxy, methoxy, benzyloxy or methylsulphenyl group; or a pyridyl group;

R_5 and R_6 together with the carbon atom between them represent an alkyidene group containing 3 to 9 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene moiety,

R_1 represents an unbranched alkyleneimino group containing 4 to 8 carbon atoms or a piperidino group mono- or disubstituted by methyl groups,

R_2 represents a hydrogen, fluorine, chlorine or bromine atom or a methyl or methoxy group; or (if R_5 and R_6 are as hereinbefore defined or R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by a methoxy or phenyl group, an n-propyl, nitrile or aminocarbonly group, an alkyl group containing 4 to 6 carbon atoms or an alkenyl group containing 3 to 5 carbon atoms) R_2 may also represent an iodine atom or a hydroxy or amino group,

R_3 represents a hydrogen or chlorine atom; and

W represents a methyl, hydroxymethyl, formyl, cyano, carboxy, carboxy-methyl, 2-carboxy-ethyl or 2-carboxy-ethenyl group, an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms wherein the alkyl component may be substituted at any carbon atom except the α-carbon atom by one or two hydroxy groups, by an alkoxy group containing 1 to 3 carbon atoms or by a pyridinecarbonyloxy group; or an alkoxycarbonyl-methyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group, wherein each alkoxy group may contain from 1 to 3 carbon atoms; and

4-[N-(6-chloro-α-phenyl-2-piperidino-benzyl)-amino-carbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof with 1 to 3 carbon atoms,
4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamic acid and C_{1-3} alkyl esters thereof,
3-[4-[(N-(α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-phenyl]-propionic acid and C_{1-3} alkyl esters thereof,
4-[N-(4-chloro-α-phenyl-2-piperidino-benzyl)-amino-carbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(3-chloro-α-phenyl-2-piperidino-benzyl)-amino-carbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-amino-carbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-amino-carbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[N-(2-(2-methyl-piperidino)-α-phenyl-benzyl)-amino-carbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(2-(3-methyl-piperidino)-α-phenyl-benzyl)-amino-carbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzaldehyde,
4-[(1-(4-fluoro-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[(1-(3-chloro-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof, and
4-[(1-(3-methyl-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

However, another group of preferred compounds are those wherein A, R_1 to R_3 and W are as hereinbefore defined, more particularly those wherein W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms in which the alkyl component may be substituted at any carbon atom except the α-carbon atom by one or two hydroxy groups, and optically active enantiomers and the salts thereof.

Particularly preferred compounds of general formula I above are those wherein

A represents a group of formula

wherein R_4 represents an n-propyl group, an alkyl group containing 4 or 5 carbon atoms, a phenyl group substituted by a methyl group or by a fluorine or chlorine atom, or a pyridyl group,

R_5 and R_6 together with the carbon atom between them represent an alkylidene group containing 3 to 5 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene part;

R_1 represents a piperidino group optionally substituted by one or two methyl groups;

R_2 represents a hydrogen, fluorine or chlorine atom or a methyl or methoxy group;

R_3 represents a hydrogen atom and

W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 4 carbon atoms;

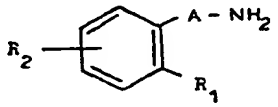
particularly those wherein

A represents a group of formula

wherein R_4 represents an n-propyl group or an alkyl group containing 4 or 5 carbon atoms and R_5 and R_6 together with the carbon atom between them represent an alkylidene group containing 3 to 5 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene part, and optically active enantiomers and salts thereof.

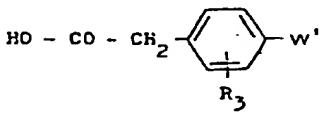
The compounds of general formula I as hereinbefore defined and their optical enantiomers and salts thereof may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

a) Reacting a compound of general formula II



(II)

(wherein A, R_1 and R_2 are as hereinbefore defined or, if A represents one of the vinylidene groups mentioned hereinbefore, the tautomers thereof or a lithium or magnesium halide complex thereof) with a compound of general formula III



(III)

(wherein R_3 is as hereinbefore defined and W' has the meanings given for W hereinbefore or represents a carboxy group protected by a protecting group), or with a reactive derivative thereof optionally formed in the reaction mixture and, if necessary, subsequently cleaving any protecting group used.

The reactive derivatives of a compound of general formula III may be, for example, the esters thereof, such as the methyl, ethyl or benzyl esters, the thio-esters thereof such as the methylthio- or ethylthio-esters, the halides thereof such as the acid chloride, or the anhydrides or imidazolides thereof.

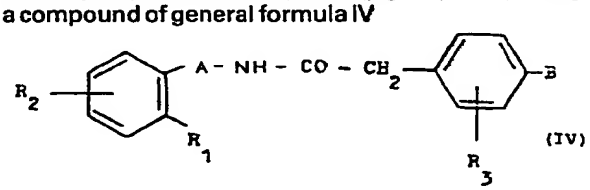
The reaction is conveniently carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an agent which activates the acid or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxy-succinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which may simultaneously serve as solvent, at temperatures of between −25°C and 250°C, but preferably at temperatures of between −10°C and the boiling temperature of the solvent used. The reaction may also be carried out without a solvent and furthermore any water formed during the reaction may be removed by azeotropic distillation, e.g. by heating with toluene using a water separator, or by the addition of a drying agent such as magnesium sulphate or a molecular sieve.

If necessary, the subsequent cleaving of a protecting group is preferably effected by hydrolysis, conveniently either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, methanol, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures of between −10°C and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

A tert.butyl group used as the protecting group may also be cleaved thermally, possibly in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic, sulphuric, phosphoric or polyphosphoric acid.

Moreover, a benzyl group used as a protecting group may also be cleaved by hydrogenolysis in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide.

b) In order to prepare a compound of general formula I wherein W represents a carboxy, carboxymethyl, 2-carboxyethyl or 2-carboxyethenyl group: subjecting a compound of general formula IV



(IV)

(wherein

R_1 to R_3 and A are as hereinbefore defined, and

B represents a group which can be converted by hydrolysis, thermolysis or hydrogenolysis into a carboxy, carboxymethyl, 2-carboxyethyl or 2-carboxyethenyl group) to hydrolysis, thermolysis or hydrogenolysis.

The hydrolysable groups in the compounds of general formula IV may be, for example, functional derivatives of carboxy, carboxymethyl, 2-carboxyethyl or 2-carboxyethenyl groups such as the unsubstituted or substituted amides thereof, the nitriles, esters, thiolesters, orthoesters, iminoethers, amidines or anhydrides thereof, a malonic ester-(1)-yl group, the tetrazolyl group, an optionally substituted 1,3-oxazol-2-yl or 1,3-oxazolin-2-yl group, and

the thermolytically cleavable groups may be, for example, esters with tertiary alcohols, e.g. the tert.butyl ester.

the hydrogenolytically cleavable groups may be, for example, esters with aralkanols, e.g. the benzyl ester.

The hydrolysis is conveniently effected either in the presence of an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of between −10°C and 120°C, e.g. at temperatures of between ambient temperature and the boiling temperature of the reaction mixture.

If B in a compound of general formula IV represents a cyano or aminocarbonyl group, these groups may also be converted into a carboxy group using a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, which is conveniently also used as the solvent, at temperatures of between 0 and 50°C.

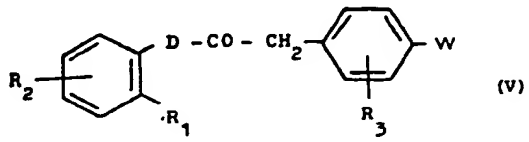
If B in a compound of general formula IV represents the tert.butyloxycarbonyl group, for example, the tert.butyl group may also be cleaved thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic, sulphuric, phosphoric or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures of between 40°C and 100°C.

If B in a compound of general formula IV represents the benzyloxycarbonyl group, for example, the benzyl group may also be cleaved hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide, preferably at temperatures of between 0 and 50°C, e.g. at ambient temperature, and at a hydrogen pressure of from 1 to 5 bar. In the hydrogenolysis, other groups may simultaneously be reduced as well (e.g. a nitro group may be reduced to an amino group, a benzyloxy group to a hydroxy group, a vinylidene group to a corresponding alkylidene group or a cinnamic acid group to the corresponding phenylpropionic acid group), or may be replaced by hydrogen atoms, e.g. a halogen atom may be replaced by a hydrogen atom.

c) In order to prepare compounds for general formula I wherein A represents a group of formula

wherein R_4' has the meanings given hereinbefore for R_4, with the exception of an alkenyl group and a cyano group:

Reduction of a compound of general formula V

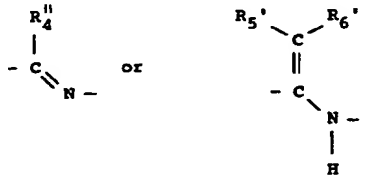


(V)

wherein

R_1 to R_3 and W are as hereinbefore defined and

D represents a group of formula



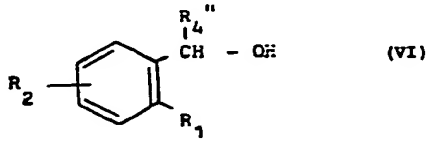
wherein R_4'' has the meanings given hereinbefore for R_4, with the exception of a cyano group and R_5' and R_6' together with the carbon atom between them represent an alkylidene group containing 1 to 7 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene moiety.

Reduction is preferably effected with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal or Raney nickel in a suitable solvent such as methanol, ethanol, isopropanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan, tetrahydrofuran, dimethylformamide, benzene or benzene/ethanol at temperatures of between 0 and 100°C, but preferably at temperatures of between 20°C and 50°C, and under a hydrogen pressure of 1 to 5 bar. When a suitable chiral hydrogenation catalyst such as a metal ligand complex is used, e.g. a complex of μ,μ'-dichloro-bis[1,5-cyclooctadiene-rhodium] and (+)- or (−) 0,0-isopropylidene-2,3-dihydroxy-1,4-bis (diphenylphosphino)-butane (= DIOP), the addition of hydrogen occurs enantioselectively. Moreover, during catalytic hydrogenation, other groups may be reduced as the same time, e.g. a nitro group may be reduced to the amino group, a benzyloxy group to the hydroxy group or a cinnamic acid group to the phenylpropionic acid group, or may be replaced by hydrogen atoms, e.g. a halogen atom may be replaced by a hydrogen atom.

d) In order to prepare compounds of general formula I wherein A represents a group of formula

wherein R_4'' has the meanings given hereinbefore for R_4, with the exception of a cyano group:

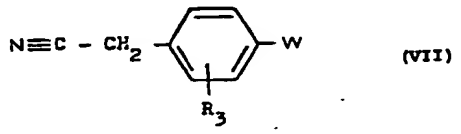
Reacting a compound of general formula VI



(VI)

(wherein

R_4'' is defined as above and R_1 and R_2 are as hereinbefore defined) with a compound of general formula VII



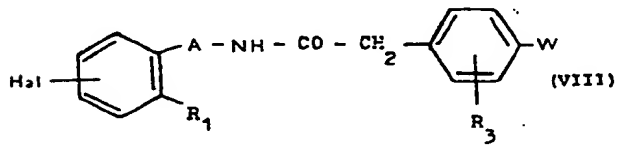
(VII)

wherein

R_3 and W are as hereinbefore defined.

The reaction is carried out in the presence of a strong acid which may simultaneously serve as solvent, preferably in concentrated sulphuric acid, at temperatures of between 0°C and 150°C, but preferably at temperatures of between 20°C and 100°C.

e) for the preparation of compounds of general formula I, wherein R_2 represents a hydrogen atom: dehalogenating a compound of general formula VIII



(VIII)

wherein

R_1, R_3, A and W are as hereinbefore defined and

Hal represents a fluorine, chlorine, bromine or iodine atom.

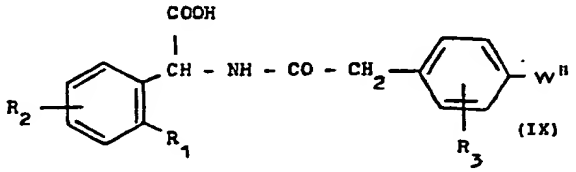
The dehalogenation is conveniently effected in a solvent such as methanol, ethanol, ethyl acetate, glacial acetic acid or dimethylformamide by means of catalytically activated hydrogen, e.g. with hydrogen in the presence of platinum or palladium / charcoal, at temperatures of between 0 and 100°C, but preferably at ambient temperature, and under a hydrogen pressure of from 1 to 5 bar. During the dehalogenation, other groups may be reduced at the same time, e.g. a benzyloxy group may be reduced to a hydroxy group, a vinylidene group to the corresponding alkylidene group or a cinnamic acid group to the corresponding phenylpropionic acid group, or may be replaced by hydrogen atoms, e.g. a halogen atom may be replaced by a hydrogen atom.

f) In order ro prepare compounds of general formula I, wherein A represents a group of formula

wherein

R_4 represents an alkyleneiminocarbonyl group containing 4 to 6 carbon atoms in the alkylene ring or an aminocarbonyl group optionally mono- or disubsituated by alkyl or phenylalkyl groups each having 1 to 3 carbon atoms in the alkyl moiety:

Reacting a compound of general formula



(IX)

(wherein

R_1, R_2 and R_3 are as hereinbefore defined and

W'' has the meanings given hereinbefore for W, with the exception of the carboxy group), with an amine of general formula X

(X)

wherein

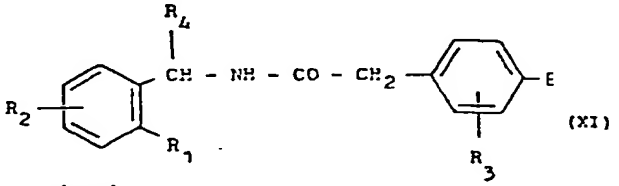
R_7 represents an alkyleneimino group containing 4 to 6 carbon atoms or an amino group optionally mono- or disubstituted by alkyl or phenylalkyl groups each having 1 to 3 carbon atoms in the alkyl moiety.

Amidation is conveniently effected in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide, preferably in the presence of an agent which activates the acid or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine which may simultaneously serve as solvent, at temperatures of between −25°C and 250°C, but preferably at temperatures of between −10°C and the boiling temperature of the solvent used.

g) In order to prepare compounds of general formula I wherein A represents a group of formula

as hereinbefore defined and W represents a carboxy group:

Oxidising a compound of general formula XI



(XI)

wherein

R_1 to R_4 are hereinbefore defined and

E represents a group which can be converted into a carboxy group by oxidation.

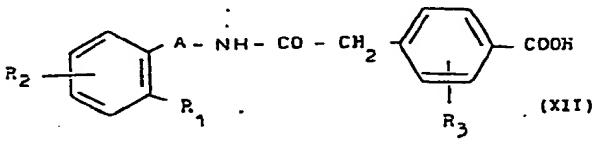
An oxidisable group of this kind may be, for example, a formyl group and the acetals thereof, a hydroxymethyl group and the ethers thereof, a

substituted or unsubstituted acyl group such as an acetyl, chloroacetyl, propionyl or malonic acid-(1)-yl group or a malonic ester-(1)-yl group.

The reaction may be carried out with an oxidising agent in a suitable solvent such as water, glacial acetic acid, methylene chloride, dioxan or glycol dimethyl ether at temperatures of between 0 and 100°C, but conveniently at temperatures of between 20°C and 50°C. However, the reaction is preferably effected with silver oxide/sodium hydroxide solution, manganese dioxide/acetone or methylene chloride, hydrogen peroxide/sodium hydroxide solution, bromine or chlorine/sodium or potassium hydroxide solution, chromium trioxide/pyridine or pyridinim chlorochromate.

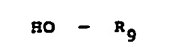
h) In order to prepare compounds of general formula I wherein W represents an alkoxycarbonyl group containing a total of 2 to 6 carbon atoms wherein the alkyl component may be substituted at any carbon atom except the α-carbon atom by one or two hydroxy groups or by an alkoxy group containing 1 to 3 carbon atoms:

Esterifying a carboxylic acid of general formula XII



(XII)

(wherein R_1 to R_3 and A are as hereinbefore defined) or a reactive derivative thereof optionally prepared in the reaction mixture,
with an alcohol of general formula XIII



(XIII)

wherein

R_9 represents an alkyl group containing 1 to 5 carbon atoms which may be substituted at any carbon atom except the α-carbon atom by one or two hydroxy groups or by an alkoxy group containing 1 to 3 carbon atoms.

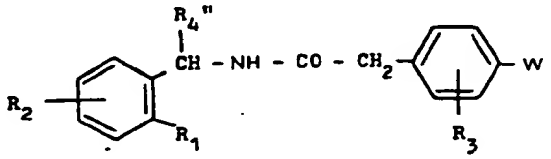
Examples of reactive derivatives of a compound of general formula XII include the halides thereof, such as the acid chloride, and the anhydrides and imidazolides.

The reaction is conveniently carried out using the corresponding alcohol as solvent or in a suitable solvent such as methylene chloride, chloroform, ether, tetrahydrofuran, dioxan, benzene or toluene, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of hydrogen chloride, sulphuric acid, ethyl chloroformate, thionyl chloride, carbon tetrachloride/triphenylphosphine, carbonyldiimidazole or N,N'-dicyclohexylcarbodiimide or the isourea ethers thereof, optionally in the presence of a reaction accelerator such as copper chloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, or by transesterification, e.g. with a corresponding carbonic acid diester, at temperatures of between −20°C and 100°C, but preferably at temperatures of between −10°C and the boiling temperature of the solvent used.

i) In order to prepare a compound of general formula I wherein W represents an alkoxycarbonyl, alkoxycarbonyl-methyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group and A represents a group of formula

where R_4'' represents R_4 as hereinbefore defined with the exception of a cyano group:

Alcoholysis of a compound of general formula XIV



(XIV)

wherein

R_4'' represents R_4 as hereinbefore defined with the exception of a cyano group and R_1 to R_3 are as hereinbefore defined and

W'' represents a cyano, cyanomethyl, 2-cyanotheyl or 2-cyanoethenyl group.

The alcoholysis is conveniently effected in a corresponding alcohol as a solvent, such as methanol, ethanol or propanol, preferably in the presence of an acid such as hydrochloric or sulphuric acid at temperatures of between 20°C and the boiling temperature of the solvent used, preferably at temperatures of between 50 and 100°C.

If, according to the invention, a compound of general formula I is initially obtained wherein W represents a carboxy or alkoxycarbonyl group, this may subsequently be converted by reduction into a corresponding compound of general formula I wherein W represents a formyl or hydroxymethyl group, and/or

if a compound of general formula I is initially obtained wherein W represents a carboxy group, this may subsequently be converted by conversion into a sulphonic acid hydrazide and subsequent disproportionation into a corresponding compound of general formula I wherein W represents a formyl group, and/or

if a compound of general formula I is initially obtained wherein W represents a formyl group, this may subsequently be converted by condensation and optional subsequent hydrolysis and/or decarboxylation into a corresponding compound of general formula I wherein W represents a 2-alkoxycarbonyl-ethenyl or a 2-carboxy-ethenyl group, and/or

if a compound of general formula I is initially obtained wherein W represents a 2-carboxy-ethenyl or 2-alkoxy-carbonyl-ethenyl group, this may subsequently be converted by catalytic hydrogenation into a corresponding compound of general formula I wherein W represents a 2-carboxyethyl or 2-alkoxycarbonyl-ethyl group, and/or

if a compound of general formula I is initially obtained wherein W represents an alkoxycarbonyl group substituted at any carbon atom except the α-carbon atom by a hydroxy group, this may subsequently be converted by acylation by means of a pyridine-

carboxylic acid into a corresponding (pyridine-carbonyloxyalkoxy)-carbonyl compound of general formula I, and/or

if a compound of general formula I is initially obtained wherein W represents a hydroxymethyl group, this may, after being converted into a corresponding halo-methyl compound, subsequently be converted by reaction with a malonic acid diester into a corresponding compound of general formula I wherein W represents an ethyl group substituted by two alkoxycarbonyl groups, and/or

if a compound of general formula I is initially obtained wherein W represents an ethyl group substituted by two alkoxycarbonyl groups, this may subsequently be converted by hydrolysis into a corresponding compound of general formula I wherein W represents an ethyl group substituted by two carboxy groups, and/or

if a compound of general formula I is initially obtained wherein W represents an ethyl group substituted by two alkoxycarbonyl groups, this may subsequently be converted by hydrolysis and decarboxylation into a corresponding compound of general formula I wherein W represents a 2-carboxyethyl group, and/or

if a compound of general formula I is initially obtained wherein R_2 represents a nitro group, this may subsequently be converted by reduction into a corresponding compound of general formula I wherein R_2 represents an amino group, and/or

if a compound of general formula I is initially obtained wherein R_2 represents an amino group, this may subsequently be converted, via a corresponding diazonium salt, into a corresponding compound of general formula I wherein R_2 represents a hydrogen or halogen atom or a hydroxy, alkoxy or alkylsulphenyl group, and/or

if a compound of general formula I is initially obtained wherein R_2 represents a hydroxy group, this may subsequently be converted by alkylation into a corresponding compound of general formula I wherein R_2 represents an alkoxy group, and/or

if a compound of general formula I is initially obtained wherein R_2 represents a benzyloxy group and/or R_4 represents an aryl group substituted by a benzyloxy group, this may subsequently be converted by debenzylation into a corresponding compound of general formula I wherein R_2 represents a hydroxy group and/or R_4 represents an aryl group substituted by a hydroxy group, and/or

if a compound of general formula I is initially obtained wherein R_4 represents an aminocarbonyl group, this may subsequently be converted by dehydration into a corresponding compound of general formula I wherein R_4 represents a cyano group.

The subsequent alcoholysis is preferably carried out in a corresponding alcohol such as ethanol, in the presence of an acid such as hydrochloric or sulphuric acid, at temperatures up to the boiling temperature of the solvent used.

The subsequent reduction is preferably carried out with a metal hydride, e.g. with a complex metal hydride such as lithium aluminium hydride, in a solvent such as diethyl ether, tetrahydrofuran or dioxan at temperatures of between 0 and 100°C, but preferably at temperatures of between 20°C and 60°C.

The subsequent disproportionation of a sulphonic acid hydrazide, which is obtained by reacting a corresponding hydrazine with a corresponding reactive carboxylic acid derivative, is carried out in the presence of a base such as sodium carbonate in a solvent such as ethyleneglycol at temperatures of between 100°C and 200°C, but preferably at 160 to 170°C.

The subsequent condensation of a formyl compound is conveniently carried out in a solvent such as pyridine or tetrahydrofuran with malonic acid, with a malonic acid ester, with a dialkylphosphono-acetic acid ester or an alkoxycarbonylmethylene-triphenyl-phosphoran, optionally in the presence of a base as the condensing agent, e.g. in the presence of piperidine, potassium tert.butoxide or sodium hydride, at temperatures of between 0 and 100°C; the desired compound is obtained by subsequent acidification, e.g. with hydrochloric or sulphuric acid, or by subsequent alkaline hydrolysis.

The subsequent catalytic hydrogenation is conveniently effected in a solvent such as methanol, ethanol, ethyl acetate, glacial acetic acid or dimethylformamide with hydrogen in the presence of a hydrogenation catalyst such as platinum or palladium/charcoal at temperatures of between 0 and 75°C, but preferably at ambient temperature and under a hydrogen pressure of 1 to 5 bar.

The subsequent O-acylation is conveniently carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide, preferably with a reactive derivative of the acid, for example a halide such as the acid chloride, and anhydride or imidazolide and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine which may simultaneously serve as solvent, at temperatures of between −25°C and 250°C, but preferably at temperatures of between −10°C and the boiling temperature of the solvent used.

The subsequent conversion of a hydroxymethyl group into a halomethyl group is effected with a halogenating agent such as thionyl chloride, phosphorus trichloride, phosphorus tribromide or phosphorus pentachloride in a solvent such as methylene chloride, carbon tetrachloride, benzene or nitrobenzene and subsequently reacting with a malonic acid ester, e.g. with an alkali metal salt of diethyl malonate, at temperatures of between 0 and 100°C, but preferably at temperatures of between 50°C and 80°C.

The subsequent hydrolysis or hydrolysis and decarboxylation is conveniently effected in the presence of an acid such as hydrochloric, sulphuric, phosphoric, polyphosphoric or trifluoroacetic acid in a suitable solvent such as water, ethanol, water/ethanol, water/isopropanol or water/dioxan at elevated temperatures, e.g. at the boiling temperature of the reaction mixture.

The subsequent reduction of the nitro compound is preferably effected in a solvent such as water, water/ethanol, methanol, glacial acetic acid, ethyl

acetate or dimethylformamide, conveniently with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid, with salts such as iron(II)sulphate, tin(II)chloride or sodium dithionite or with hydrazine in the presence of Raney nickel at temperatures of between 0 and 50°C, but preferably at ambient temperature.

The subsequent reaction of a diazonium salt, e.g. the fluoroborate, the fluoride in 40% hydrofluoric acid, the hydrosulphate in sulphuric acid or the hydrochloride, if necessary in the presence of copper or a corresponding copper(I)salt such as copper(I)chloride/hydrochloric acid or copper(I)bromide/hydrobromic acid, is carried out at slightly elevated temperatures, e.g. at temperatures of between 15°C and 100°C; the subsequent reaction with hypophosphorous acid is preferably carried out at −5°C to 0°C. The diazonium salt required is conveniently prepared in a suitable solvent, e.g. in water/hydrochloric acid, methanol/hydrochloric acid, ethanol/hydrochloric acid or dioxan/hydrochloric acid, by diazotising a corresponding amino compound with a nitrite, e.g. sodium nitrite or an ester of nitrous acid, at low temperatures, e.g. at temperatures of between −10°C and 5°C.

The subsequent O - alkylation is conveniently effected with a corresponding halide, sulphonic acid ester or diazoalkane, e.g. with methyl iodide, dimethylsulphate, ethyl bromide, ethyl p - toluenesulphonate, isopropylmethanesulphonate or diazomethane, optionally in the presence of a base such as sodium hydride, potassium hydroxide or potassium tert.butoxide and preferably in a solvent such as diethyl ether, tetrahydrofuran, dioxan, methanol, ethanol, pyridine or dimethylformamide at temperatures of between 0 and 75°C, preferably at ambient temperature.

The subsequent debenzylation is conveniently effected in a solvent such as methanol, ethanol, ethyl acetate, glacial acetic acid or dimethylformamide using catalytically acitvated hydrogen, e.g. using hydrogen in the presence of platinum or palladium/charcoal, at temperatures of between 0 and 75°C, but preferably at ambient temperatures and at a hydrogen pressure of from 1 to 5 bar.

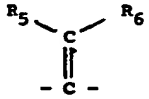
The subsequent dehydration is carried out with a dehydrating agent such as phosphorus pentoxide, sulphuric acid or p - tolrenesulphonic acid chloride, optionally in a solvent such as methylene chloride or phyridine at temperatures of between 0 and 100°C, preferably at temperatures of between 20° and 80°C.

If they have a chiral centre, the compounds of general formula I obtained can also be resolved into their enantiomers by conventional methods. This may, for example, be effected by column chromatography on a chiral phase.

A compound of general formula I or a tautomer thereof, initially obtained, may subsequently be converted into an addition salt thereof, of example by conventional methods such as reacting the compound of general formula I or tautomer thereof as a base with an acid in a suitable solvent, or reacting the compound of general formula I or tautomer thereof as an acid with a base in a suitable solvent. A salt of a compound of general formula I or a tautomer thereof, initially obtained, may subsequently be converted by conventional methods into a different salt or into a compound of general formula I or tautomer thereof.

The compounds of general formulae II to XIV used as starting materials may be obtained by methods known from the literature or are themselves known from the literature.

Thus, for example, a compound of general formula II wherein A represents a group of formula



or the tautomeric ketimine thereof is obtained by reacting a corresponding nitrile with a corresponding Grignard or lithium compound and subsequently hydrolysing or by reacting a corresponding ketone with ammonia in the presence of titanium tetrachloride. For further reaction with a compound of general formula III or the reactive derivatives thereof, more particularly the acid chlorides thereof, it is also possible to use the organometallic ketimine complex.

A compound of the general formula II wherein A represents a group of formula

wherein R_4''' has the meanings given hereinbefore for R_4 with the exception of the cyano and aminocarbonyl groups, is obtained, for example, by reacting a corresponding nitrile with a corresponding Grignard or lithium compound and optionally subsequently carrying out lithium aluminium hydride reduction or subsequent hydrolysis to form the ketimine, which is then reduced with catalytically activated hydrogen, with a complex metal hydride or with nascent hydrogen, by hydrolysis or hydrazinolysis of a corresponding phthalimido compound, by reacting a corresponding ketone with ammonium formate and subsequent hydrolysis or with an ammonium salt in the presence of sodium cyanoborohydride, by reduction of a corresponding oxime with lithium aluminium hydride or with catalytically activated or nascent hydrogen, by reduction of a corresponding N-benzyl- or N - (1 - phenylethyl) - ketimine, e.g. with catalytically activated hydrogen or with a complex metal hydride in ether of tetrahydrofuran at temperatures of between −78°C and the boiling temperature of the solvent used and subsequently cleaving the benzyl or 1-phenylethyl group by catalytic hydrogenation, by Ritter reaction of a corresponding alcohol with potassium cyanide in sulphuric acid, or by Hofmann, Curtius, Lossen or Schmidt degradation of a corresponding compound.

A compound of general formula II wherein A represent the group

may be obtained by reacting a corresponding aldehyde with ammonium cyanide or by reacting a corres-

ponding cyanohydrin with ammonia.

An amine of general formula II thus obtained, having a chiral centre, wherein A represents a group of formula

wherein R_4" has the meanings given hereinbefore with the exception of the cyano group, may be resolved into the enantiomers by racemate splitting, e.g. by fractional crystallisation of the diastereomeric salts with optially active acids and subsequent decomposition of the salts or by column chromatography on a chiral phase, or by forming diastereomeric compounds and then separating and splitting them.

Moreover, an optically active amine of general formula II may also be prepared by enantioselective reduction of a corresponding ketimine using complex boron or aluminium hydrides wherein some of the hydride hydrogen atoms are replaced by optically active alkoxide radicals, or by means of hydrogen in the presence of a suitable chiral hydrogenation catalyst or analogously, starting from a corresponding N-benzyl- or N-(1-phenethyl)-ketimine or from a corresponding N-acyl-ketimine or enamide and optionally subsequently cleaving the benzyl, 1-phenethyl or acyl group.

Furthermore, an optically active amine of general formula II may also be prepared by diastereoselective reduction of a corresponding ketimine or hydrazone chirally substituted at the nitrogen atom, by means of complex or non-complex boron of aluminium hydrides wherein, if desired, some of the hydride hydrogen atoms have been replaced by corresponding alkoxide, phenolate or alkyl radicals, or by means of hydrogen in the presence of a suitable hydrogenation catalyst and optional subsequent cleaving of the chiral auxlaliary radical by catalytic hydrogenolysis or hydrolysis.

In addition, an optically active amine of general formula II may also be prepared by diastereoselective addition of a corresponding organometallic compound, preferably a Gringnard or lithium compound, to a corresponding aldimine chirally substituted at the nitrogen atom, by subsequent hydrolysis and optional subsequent cleaving of the chiral auxillary radical by catalytic hydrogenolysis or hydrolysis.

The compounds of general formulae IV, VIII, IX, XI, XII and XIV used as starting materials are obtained by reacting a corresponding amine with a corresponding compound of general formula III or the reactive derivatives thereof, with optional subsequent hydrolysis.

A compound of general formula V used as starting material is preferably obtained by acylating a corresponding ketimine of the organometallic complex thereof with a corresponding carboxylic acid or the reactive derivatives thereof.

As already mentioned hereinbefore, the new compounds of general formula I as hereinbefore defined, the tautomers and optical enantiomers thereof and acid and base addition salts of the aforementioned compounds have valuable pharmacological properties, namely an effect on the intermediate metabolism, but particularly the hypoglycaemic effect of lowering blood sugar and, to some extent, an effect on the cardiac circulatory system.

For example, the following compounds have been examined for their properties as follows:

A = (Z)-4-[(1-(2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid,

B = ethyl (Z)-4-[(1-(2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoate,

C = (E)-4-[(1-(2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid,

D = 4-[(2-methyl-1-(2-piperidino-phenyl)-1-propen-1-yl)-aminocarbonylmethyl]-benzoic acid,

E = ethyl (Z)-4-[(1-(2-piperidino-phenyl)-1-hexen-1-yl)-aminocarbonylmethyl]-benzoate,

F = (Z)-4-[(3-phenyl-1-(2-piperidino-phenyl)-1-propen-1-yl)-aminocarbonylmethyl]-benzoic acid,

G = (Z)-4-[(1-(2-(3,3-dimethyl-piperidino)-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid,

H = 4-[(1-(2-pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

J = (±)-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

K = (+)-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

L = ethyl (+)-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate,

M = 4-[(1-(2-hexahydroazepino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

N = 4-[(1-(2-piperidino-phenyl)-1-hexyl)-aminocarbonylmethyl]-benzoic acid,

O = 4-[(3-phenyl-1-(2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoic acid,

P = 4-[(2-methoxy-1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid,

Q = 4-[(α-cyano-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

R = 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl alcohol,

S = 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenylacetic acid,

T = 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid,

U = 2,3-dihydroxy-propyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate,

V = 4-[(1-(4-fluoro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

W = 4-[(1-(4-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid,

X = 4-[(1-(2-octahydroazonino-phenyl)-1-ethenyl)-aminocarbonylmethyl]-benzoic acid,

Y = 4-[(1-(3-chloro-2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid,

Z = 4-[(1-(3-methyl-2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid,

AA = 4-[(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

AB = 4-[(α-(3-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

AC = 4-[(α-(4-fluoro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

AD = 4-[(α-(2-fluoro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,

AE = 4-[(α-(4-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
AF = 4-[(α-(3-chloro-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
AG = 4-[(2-piperidino-α-(2-pyridyl)-benzyl)-aminocarbonylmethyl]-benzoic acid,
AH = 4-[(2-piperidino-α-(4-pyridyl)-benzyl)-aminocarbonylmethyl]-benzoic acid,
AJ = 4-[(6-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
AK = 4-[(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamic acid,
AL = 3-[4-[(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid,
AM = 4-[(4-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
AN = 4-[(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
AO = 4-[(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid,
AP = 4-[(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzaldehyde,
AQ = 4-[(2-(2-methyl-piperidino)-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid,
AR = 4-[(2-(3-methyl-piperidino)-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid and
AS = 4-[(3-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid:

1. *Hypoglycaemic activity*

The hypoglycaemic activity of the test substances was tested on female rats of a single strain weighing from 180 to 220 g, which had been kept without food or drink for 24 hours before the start of the test. The substances to be tested were suspended in 1.5% methylcellulose immediately before the start of the test and administered by oesophageal tube.

Blood samples were taken immediately before the administration of the substance and then 1, 2, 3 and 4 hours afterwards, in each case from the retro-orbital venous plexus. From each sample, 50 µl were deproteinated with 0.5 ml of 0.33 N perchloric acid and then centrifuged. The glucose in the supernatant phase was determined by the hexokinase method using an analytical photometer. The results were evaluated statistically using the t test according to Student, taking $p = 0.05$ as the limit of significance.

The following Table contains the values found in percent, compared with the controls:

Substance	5 mg/kg 1	2	3	4	1 mg/kg 1	2	3	4
A					-43	-40	-33	-35
B	-44	-39	-26	-35	-39	-19	-26	-30
C					-43	-43	-37	-38
D					-36	-32	-27	-25
E	-46	-40	-38	-26	-23	-23	-12	-18
F	-43	-42	-39	-32				
G					-44	-42	-37	-31
H	-50	-46	-44	-45				
J	-44	-37	-42	-42	-38	-32	-34	-29
K					-41	-43	-38	-31
L	-42	-45	-31	-22	-14	-18	-14	n.s.
M	-46	-43	-40	-36	-33	-30	-21	n.s.
N	-42	-42	-37	-33				
O	-38+	-31+	n.s.+	n.s.+				
P	-49	-43	-34	-22	-37	-19	n.s.	n.s.
Q	-28	-13	n.s.	n.s.				
R	-38	-40	-35	-29	-39	-34	-29	-24
S	-49	-42	-30	-17	-29	-20	-10	n.s.
T	-48	-46	-42	-40	-42	-42	-40	-32
U	-43	-43	-49	-45	-39	-35	-29	-24
V	-45	-41	-46	-40	-37	-23	-30	-18
W	-46	-45	-39	-37	-36	-25	-16	n.s.
X	-34+	-21+	-17+	-14+				
Y	-32	-24	-16	-18				
Z	-22	-33	-28	-26				
AA	-30	-33	-14	n.s.	-15	-15	-13	n.s.
AB	-43	-38	-36	-27	-26	-15	n.s.	n.s.
AC	-36	-37	-36	-33				
AD	-28	-32	-27	-28	-16	-20	-17	-14
AE	-30	-28	-39	-36	-21	-20	-22	n.s.

Substance	5 mg/kg 1	2	3	4	1 mg/kg 1	2	3	4
AF	-43	-39	-30	-26	-17	-19	n.s.	n.s.
AG	-49+	-50+	-36+	-31+	-18	n.s.	n.s.	n.s.
AH	-41	-37	-20	n.s.	-26	-14	n.s.	n.s.
AJ	-44	-40	-39	-40	-35	-34	-28	-20
AK	-48+	-47+	-40+	-45+	-32	-19	-10	-17
AL	-43+	-41+	-38+	-34+	-40	-31	-23	-12
AM	-34	-35	-32	-29	-11	-13	n.s.	n.s.
AN	-39	-35	-27	-26	-27	-24	n.s.	n.s.
AO	-37	-34	-32	-31	-21	-17	-15	-11
AP					-26	-28	-22	-17
AQ	-32	-31	-24	-19	-16	-11	n.s.	n.s.
AR	-35	-30	-29	-31	-13	- 9	n.s.	n.s.
AS	-45	-44	-42	-32	-21	-13	n.s.	n.s

+ = at 10 mg/kg
n.s. = statistically not significant

2. *Acute toxicity*

The toxic effect was tested in male and female mice of the same strain weighing from 20 to 26 g, after oral administration of a single dose (suspended in 1% methylcellulose) over an observation period of 14 days:

Substance	Approximate acute toxicity
A	> 1 000 mg/kg p.o. (0 out of 6 animals died)
C	> 2 000 mg/kg p.o. (0 out of 6 animals died)
D	> 500 mg/kg p.o. (0 out of 6 animals died)
J	> 2 000 mg/kg p.o. (0 out of 10 animals died)
AA	> 1 000 mg/kg p.o. (0 out of 10 animals died)
AB	> 1 000 mg/kg p.o. (0 out of 10 animals died)
AC	> 1 000 mg/kg p.o. (0 out of 10 animals died)
AD	> 1 000 mg/kg p.o. (0 out of 10 animals died)
AE	> 1 000 mg/kg p.o. (0 out of 10 animals died)
AG	> 1 000 mg/kg p.o. (0 out of 10 animals died)

In view of their pharmacological properties, the compounds prepared according to the invention are suitable for the treatment of diabetes mellitus.

According to a yet further feature of the present invention, we provide pharmaceutical compositions comprising, as active ingredient, at least one compound of general formula I as hereinbefore defined or a tautomer thereof or a physiologically compatible salt of these compounds, in association with one or more pharmaceutical carriers or excipients.

For pharmaceutical administration the compounds of general formula I or tautomers thereof or their phsiologically compatible salts may be incorporated into conventional preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral or parenteral administration. Preferred forms include, for example, tablets, coated tablets, capsules, powders or suspensions.

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, corn starch, lactose, celulose, magnesium stearate, citric acid, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously, the compositions may be formulated as dosage units, each dosage unit being adapted to supply a fixed dose of active ingredient.

A suitable single dose for adults is 1-50 mg, preferably 2.5-20 mg of active ingredient, once or twice per day. The total daily dosage may, however, be varied according to the compounds used, the subject treated and the complaint concerned.

According to a still further feature of the present invention, we provide a method of treating a patient suffering from or susceptible to diabetes mellitus or disorders of the intermediate metabolism or the cardiac circulatory system, which comprises administering to the said patient an effective amount of a compound of general formula I as hereinbefore defined or a tautomer thereof or a physiologically compatible salt thereof.

The following non-limiting Examples are intended to illustrate the invention:

Example 1

Ethyl 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate

4.7 g (18 mmol) of triphenylphosphine, 3 g (30 mmol) of triethylamine and 1.5 mm (15 mmol) of

carbon tetrachloride are added successively to 4.2 g (15 mmol) of α-(4-methyl-phenyl)-2-piperidino-benzylamine and 3.4 g (16.5 mmol) of 4-ethoxycarbonyl-phenylacetic acid, dissolved in 40 ml of acetonitrile. The reaction mixture is stirred at 50°C for 2 hours, then concentrated by evaporation and, after acidification with 6N hydrochloric acid, extracted with ethyl acetate. The acidic aqueous phase is then extracted several times with methylene chloride. The methylene chloride extracts are washed with sodium bicarbonate solution, dried over magnesium sulphate and concentrated by evaporation. The evaporation residue is triturated with ethanol and suction filtered.

Yield: 4.55 g (65% of theory),
M.p.: 177-178°C
Calculated: C 76.57 H 7.28 N 5.95
Found: C 76.19 H 7.16 N 5.82

The following were prepared analogously to Example 1:

(a) Ethyl 4-[N-(α-(3-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonyl-methyl]-benzoate
Yield: 48% of theory,
M.p.: 159-160°C
Calculated: C 76.57 H 7.28 N 5.95
Found: C 76.80 H 7.35 N 5.76

(b) Ethyl 4-[N-[α-(2-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 35.4% of theory,
M.p.: 196-198°C
Calculated: C 76.57 H 7.28 N 5.95
Found: C 76.65 H 7.35 N 5.90

(c) Ethyl 4-[N-[α-(4-methoxy-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 45% of theory,
M.p.: 167-168°C
Calculated: C 74.05 H 7.04 N 5.76
Found: C 73.72 H 6.99 N 5.62

(d) Ethyl 4-[N-[α-(4-benzyloxy-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 96% of theory,
M.p.: 154-155°C
Calculated: C 76.84 H 6.81 N 4.98
Found: C 76.68 H 6.68 N 5.03

(e) Ethyl 4-[N-[α-(4-fluoro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl] benzoate
Yield: 58% of theory,
M.p.: 174-176°C
Calculated: C 73.40 H 6.58 N 5.90
Found: C 73.55 H 6.72 N 5.91

(f) Ethyl 4-[N-[α-(2-fluoro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 83% of theory,
M.p.: 173-175°C
Calculated: C 73.40 H 6.58 N 5.90
Found: C 73.61 H 6.62 N 5.85

(g) Ethyl 4-[N-[α-(4-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 57% of theory,
M.p.: 178-181°C
Calculated: C 70.94 H 6.36 N 5.71 Cl 7.22
Found: C 71.10 H 6.56 N 5.26 Cl 7.11

(h) Ethyl 4-[N-[α-(3-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 71% of theory,
M.p.: 153-156°C
Calculated: C 70.94 H 6.36 N 5.71 Cl 7.22
Found: C 70.86 H 6.26 N 5.65 Cl 7.25

(i) Ethyl 4-[N-[α-(2-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 66% of theory,
M.p.: 196-198°C
Calculated: C 70.94 H 6.36 N 5.71 Cl 7.22
Found: C 70.90 H 6.30 N 5.61 Cl 7.10

(k) Ethyl 4-[N-[α-(4-methylmercapto-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 84% of theory,
M.p.: 173-175°C
Calculated: C 71.68 H 6.82 N 5.57 Cl 6.38
Found: C 71.92 H 6.97 N 5.45 Cl 6.21

(l) Ethyl 4-[N-[5-chloro-α-(2-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 92% of theory,
M.p.: 213-215°C
Calculated: C 66.28 H 5.75 N 5.33 Cl 13.49
Found: C 66.45 H 5.86 N 5.25 Cl 13.51

(m) Ethyl 4-[N-[2-piperidino-α-(2-pyridyl)-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 51% of theory,
M.p.: 158-159°C
Calculated: C 73.50 H 6.83 N 9.18
Found: C 73.40 H 6.95 N 9.10

(n) Ethyl 4-[N-[2-piperidino-α-(3-pyridyl)-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 85% of theory,
M.p.: 172°C
Calculated: C 73.50 H 6.83 N 9.18
Found: C 73.42 H 6.76 N 9.25

(o) Ethyl 4-[N-[2-piperidino-α-(4-pyridyl)-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 20% of theory,
M.p.: 150-152°C
Calculated: C 73.50 H 6.83 N 9.18
Found: C 73.61 H 6.91 N 9.15

(p) Ethyl 4-[N-(6-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 12% of theory,
M.p.: Oil
Calculated: molecular ion peak m/e = 490/492
Found: molecular ion peak m/e = 490/492

(q) Ethyl 4-[N-(4-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 37% of theory,
M.p.: 148-150°C
Calculated: C 70.94 H 6.36 N 5.71 Cl 7.22
Found: C 70.81 H 6.25 N 5.61 Cl 7.12

(r) Ethyl 4-[N-(3-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 74% of theory,
M.p.: 176-178°C

Calculated: C 70.94 H 6.36 N 5.71 Cl 7.22
Found: C 70.59 H 6.25 N 5.68 Cl 7.16
(s) Ethyl 4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 65% of theory,
M.p. Oil
Calculated: molecular ion peak m/e = 470
Found: molecular ion peak m/e = 470
(t) Ethyl 4-[N-(5-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 48% of theory,
M.p.: 171-173°C
Calculated: C 76.57 H 7.28 N 5.95
Found: C 76.75 H 7.35 N 5.72
(u) Ethyl 4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 76% of theory,
M.p.: 133-135°C
Calculated: C 76.57 H 7.28 N 5.95
Found: C 76.51 H 7.16 N 5.83
(v) Ethyl 4-[N-(5-methoxy-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 10% of theory,
M.p. 122-125°C
Calculated: molecular ion peak m/e = 486
Found: molecular ion peak m/e = 486
(w) Ethyl 4-[N-(6-methoxy-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 97% of theory,
M.p. Oil
Calculated: molecular ion peak m/e = 486
Found: molecular ion peak m/e = 486
(x) Ethyl 3-chloro-4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 42% of theory,
M.p.: 175-176°C
Calculated: C 70.93 H 6.36 N 5.71 Cl 7.22
Found: C 70.65 H 6.36 N 5.50 Cl 7.29
(y) Ethyl 4-[N-(2-dimethylamino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 67% of theory,
M.p.: 116-118°C
Calculated: C 74.97 H 6.77 N 6.73
Found: C 75.13 H 6.60 N 6.78
(z) Ethyl 4-[N-(2-di-n-propylamino-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate
Yield: 76% of theory,
M.p.: 38-139°C
Calculated: C 76.24 H 7.68 N 5.93
Found: C 76.41 H 7.79 N 5.81
(aa) Ethyl 4-[N-[2-octahydro-1H-azonino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 71% of theory
M.p.: Oil
Calculated: molecular ion peak m/e = 498
Found: molecular ion peak m/e = 498
(ab) Ethyl 4-[N-[5-chloro-2-(2-methyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 36.5% of theory
M.p.: 171-173°C
Calculated: C 71.24 H 6.58 N. 5.54 Cl 7.01
Found: C 71.45 H 6.68 N 5.59 Cl 7.20.
(ac) Ethyl 4-[N-[2-(3,3-dimethyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 91% of theory,
M.p.: 146-148°C
Calculated: C 76.82 H 7.49 N. 5.78
Found: C 76.91 H 7.55 N 5.61

Example 2

Ethyl 4-[N-[α-(4-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonyl-methyl]-benzoate

A solution of 5 g (22.1 mmol) of 4-ethoxycarbonylphenylacetyl chloride in 20 ml of chloroform is added dropwise, whilst cooling with ice, to a solution of 6.02 g (20 mmol) of α-(4-chloro-phenyl)-2-piperidino-benzylamine and 3.5 ml (25 mmol) of triethylamine in 50 ml of chloroform. The mixture is stirred for 2 hours at ambient temperature then added to water and extracted with chloroform. The extracts are dried and concentrated by evaporation. The evaporation residue is chromatographed on silica gel using toluene/ethyl acetate (5:1) as eluant.
Yield: 5.6 g (57% of theory),
M.p.: 178-181°C
Calculated: C 70.94 H 6.36 N 5.71 Cl 7.22
Found: C 71.09 H 6.47 N 5.61 Cl 7.10

The following was prepared analogously to Example 2:
(a) Ethyl 4-[N-[5-chloro-2-(3-methyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoate
Yield: 54% of theory,
M.p.: 178-180°C
Calculated: C 71.24 H 6.58 N 5.54 Cl 7.01
Found: C 70.91 H 6.64 N 5.75 Cl 7.01

Example 3

4-[N-α-(4-methyl-phenyl)-2-piperidino-benzyl] aminocarbonyl-methyl] benzoic acid

4.4 g (9.35 mmol) of ethyl 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate are dissolved in 150 ml of ethanol, with heating. Then 20 ml of 1N sodium hydroxide solution are added and the mixture is stirred for 3 hours at 50°C. 20 ml of 1N hydrochloric acid are then added to the reaction mixture and any excess ethanol is eliminated by evaporation in a rotary evaporator. The remaining aqueous suspension is filtered and the precipitate is thoroughly washed with water. It is then recrystallised from acetonitrile.
Yield: 2.45 g (59.3% of theory)
M.p.: 226-228°C
Calculated: C 75.99 H 6.83 N 6.33
Found: C 75.60 H 6.75 N 6.29

The following were prepared analogously to Example 3:
(a) 4-[N-[α-(3-Methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 72% of theory
M.p.: 202-203°C
Calculated: C 75.99 H 6.83 N 6.33
Found: C 75.64 H 6.91 N 6.37
(b) 4-[N-[α-(2-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 42.6% of theory,
M.p.: 285-290°C
Calculated: C 75.99 H 6.83 N 6.33
Found: C 76.05 H 6.98 N 6.25

(c) 4-[N-[α-(4-methoxy-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 72.4 of theory,
M.p.: 228-230°C
Calculated: C 73.34 H 6.59 N 6.11
Found: C 73.22 H 6.61 N 6.13
(d) 4-[N-[α-(4-benzyloxy-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 57% of theory,
M.p. 219-221°C
Calculated: C 76.38 H 6.41 N 5.24
Found: C 76.05 H 6.44 N 5.24
(e) 4-[N-[α-(4-fluoro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl] benzoic acid
Yield: 75% of theory,
M.p.: 238-240°C
Calculated: 72.63 H 6.09 N 6.27
Found: C 72.98 H 6.29 N 6.32
(f) 4-[N-[α-(2-fluoro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 87% of theory,
M.p.: 280-283°C
Calculated: C 72.63 H 6.09 N 6.27
Found: C 72.70 H 6.10 N 6.37
(g) 4-[N-[α-(4-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 89% of theory,
M.p.: 241-242°C
Calculated: C 70.05 H 5.88 N 6.05 Cl 7.66
Found: C 69.74 H 6.05 N 6.01 Cl 7.64
(h) 4-[N-[α-(3-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 53% of theory,
M.p.: 223-225°C
Calculated: C 70.05 H 5.88 N 6.05 Cl 7.66
Found: C 70.28 H 5.98 N 5.78 Cl 7.84
(i) 4-[N-[α-(2-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 98% of theory,
M.p.: 303-305°C
Calculated: C 70.05 H 5.88 N 6.05 Cl 7.66
Found: C 69.88 H 6.05 N 5.87 Cl 7.74
(k) 4-[N-[α-(4-methylmercapto-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 84.6% of theory,
M.p. 225-227°C
Calculated: C 70.86 H 6.37 N 5.90 Cl 6.75
Found: C 70.34 H 6.37 N 5.68 Cl 6.82
(l) 4-[N-[5-chloro-α-(2-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 90% of theory,
M.p.: 317-320°C
Calculated: C 65.19 H 5.27 N 5.63 Cl 14.25
Found: C 64.87 H 5.34 N 5.69 Cl 14.22
(m) 4-[N-[2-piperidino-α-(2-pyridyl)-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 81% of theory,
M.p.: 160-161°C
Calculated: C 72.71 H 6.34 N 9.78
Found: C 72.43 H 6.39 N 10.00
(n) 4-[N-(2-piperidino-α-(3-pyridyl)-benzyl]-aminocarbonxylmethyl]-benzoic acid
Yield: 72% of theory,
M.p.: 252-253°C
Calculated: C 72.71 H 6.34 N 9.78
Found: C 72.56 H 6.53 N 9.60
(o) 4-[N-[2-piperidino-α-(4-pyridyl)-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 68.5% of theory,
M.p.: from 260°C (decomposition)
Calculated: C 72.71 H 6.34 N 9.78
Found: C 72.31 H 6.29 N 9.63
(p) 4-[N-(6-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 82% of theory,
M.p.: 91-94°C
Calculated: C 70.04 H 5.88 N 6.05 Cl 7.66
Found: C 69.61 H 5.77 N 5.96 Cl 7.78
(q) 4-[N-(4-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 61% of theory,
M.p.: 221-223°C
Calculated: C 70.05 H 5.88 N 6.05 Cl 7.66
Found: C 69.73 H 5.89 N 5.87 Cl 7.52
(r) 4-[N-(3-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 83% of theory,
M.p.: 210-213°C
Calculated: C 70.05 H 5.88 N 6.05 Cl 7.66
Found: C 70.31 H 6.03 N 5.90 Cl 7.79
(s) 4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 64% of theory,
M.p.: 165-170°C (sintering from 150°C)
Calculated: C 75.99 H 6.83 N 6.33
Found: C 75.73 H 6.96 N 6.14
(t) 4-[N-(5-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 97% of theory,
M.p.: 243-245°C
Calculated: C 75.99 H 6.83 N 6.33
Found: C 75.60 H 7.01 N 6.31
(u) 4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 96% of theory,
M.p.: 202-203°C
Calculated: C 75.99 H 6.83 N 6.33
Found: C 76.04 H 6.78 N 6.23
(v) 4-[N-(5-methoxy-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 27% of theory,
M.p.: 217-220°C (sintering from 203°C)
Calculated: C 73.34 H 6.59 N 6.11
Found: C 72.92 H 6.68 N 5.99
(w) 4-[N-(6-methoxy-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 51.5% of theory,
M.p.: 90-95°C
Calculated: C 73.34 H 6.59 N 6.11
Found: C 73.03 H 6.42 N 5.86
(x) 4-[N-[5-chloro-2-(3,5-cis-dimethyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoic acid
Yield: 81% of theory,
M.p.: 253-255°C
Calculated: C 70.93 H 6.36 N 5.71 Cl 7.22
Found: C 70.68 H 6.51 N 5.73 Cl 7.36
(y) 4-[N-(2-dimethylamino-α-phenyl-benzyl)-

aminocarbonylmethyl] - benzoic acid
Yield: 83% of theory,
M.p.: 183-184°C
Calculated: C 74.20 H 6.23 N 7.21
Found: C 74.31 H 6.27 N 7.16
(z) 4 - [N - (2 - di - n - propylamino - α - phenyl - benzyl) - aminocarbonylmethyl] - benzoic acid
Yield: 79% of theory,
M.p.: 202-204°C
Calculated: C 75.64 H 7.26 N 6.30
Found: C 75.74 H 7.31 N 6.15
(aa) 4 - [N - [5 - chloro - 2 - (2 - methyl - piperidino) - α - phenyl - benzyl] - aminocarbonylmethyl] - benzoic acid
Yield: 52% of theory,
M.p.: 280-282°C
Calculated: C 70.50 H 6.13 N 5.87 Cl 7.43
Found: C 70.14 H 6.10 N 5.75 Cl 7.45
(ab) 4 - [N - [5 - chloro - 2 - (3 - methyl - piperidino) - α - phenyl - benzyl] - aminocarbonylmethyl] - benzoic acid
Yield: 66% of theory,
M.p.: 246-248°C
Calculated: C 70.50 H 6.13 N 5.87 Cl 7.43
Found: C 70.16 H 6.07 N 5.87 Cl 7.30
(ac) 4 - [N - [2 - (3,3 - dimethyl - piperidino) - α - phenyl - benzyl] - aminocarbonylmethyl] - benzoic acid
Yield: 59% of theory,
M.p.: 238-240°C
Calculated: C 76.28 H 7.07 N 6.14
Found: C 76.38 H 7.28 N 6.11
(ad) 3 - chloro - 4 - [N - (α - phenyl - 2 - piperidino - benzyl) - aminocarbonylmethyl) - benzoic acid
Yield: 56% of theory,
M.p.: 236-239°C
Calculated: C 70.04 H 5.88 N 6.05 Cl 7.66
Found: C 69.88 H 5.77 N 5.86 Cl 7.81
(ae) 4 - [N - [2 - (3,5 - cis - dimethyl - piperidino) - 5 - nitro - α - phenyl - benzyl] - aminocarbonylmethyl] - benzoic acid
Yield: 81% of theory,
M.p.: from 255°C (decomposition)
Calculated: C 69.44 H 6.23 N 8.38
Found: C 68.95 H 6.44 N 8.53
(af) 4 - [N - [2 - (octohydro - 1H - azonino) - α - phenyl - benzyl] - amino - carbonylmethyl] - benzoic acid
Yield: 62.5% of theory,
M.p.: 235-237°C
Calculated: C 76.56 H 7.28 N 5.95
Found: C 76.50 H 7.30 N 5.94
(ag) 4 - [N - (5 - hydroxy - α - phenyl - 2 - piperidino - benzyl) - amino - carbonylmethyl] - benzoic acid
Yield: 71% of theory,
M.p.: 98-101°C
Calculated: C 72.95 H 6.35 N 6.30
Found: C 72.98 H 6.40 N 6.47

Example 4

4 - [N - [α - (4 - hydroxy - phenyl) - 2 - piperidino - benzyl] - amino - carbonyl - methyl] - benzoic acid

1.1 g (2 mmol) of 4 - [N - [α - (4 - benzyloxy - phenyl) - 2 - piperidino - benzyl] - aminocarbonylmethyl] - benzoic acid are suspended in 200 ml of ethanol and catalytically debenzylated at 50°C, under a hydrogen pressure of 5 bar, in the presence of 0.4 g of 10% palladium/charcoal. Then the catalyst is filtered off, and the filtrate is concentrated by evaporation and recrystallised from acetonitrile.
Yield: 720 mg (66.7% of theory),
M.p.: 202-204°C
Calculated: C 72.95 H 6.35 N 6.30
Found: C 72.65 H 6.17 N 6.20
The following was prepared analogously to Example 4:
(a) Ethyl 4 - [N - (5 - hydroxy - α - phenyl - 2 - piperidino - benzyl) - aminocarbonylmethyl] - benzoate
Yield: 93% of theory,
M.p.: 191-193°C
Calculated: C 73.70 H 6.82 N 5.93
Found: C 73.52 H 6.57 N 5.61

Example 5

4 - [N - [α - (4 - Methyl - phenyl) - 2 - piperidino - benzyl] - aminocarbonylmethyl] - benzyl alcohol

2.5 g (5.3 mmol) of ethyl 4 - [N - [α - (4 - methyl - phenyl) - 2 - piperidino - benzyl] - aminocarbonylmethyl] - benzoate are added in batches to a suspension of 0.5 g (13.2 mmol) of lithium aluminium hydride in 50 ml of absolute tetrahydrofuran. The mixture is stirred for a further 30 minutes at ambient temperature, decomposed by the dropwise addition of 4 N sodium hydroxide solution and filtered to remove the sodium aluminate formed. The filtrate is concentrated by evaporation and the residue is recrystallised from a little toluene.
Yield: 0.98 g (43% of theory)
M.P. 144-146°C
Calculated: C 78.47 H 7.53 N 6.54
Found: C 78.20 H 7.39 N 6.58
The following was prepared analogously to Example 5:
(a) 4 - [N - [α - phenyl - 2 - piperidino - benzyl] - aminocarbonylmethyl] - benzyl alcohol
Yield: 31.5% of theory
M.p. 143-145°C
Calculated: C 78.23 H 7.29 N 6.76
Found: C 78.13 H 7.30 N 6.62

Example 6

4 - [N - [α - (4 - methyl - phenyl) - 2 - piperidino - benzyl] - amino - carbonyl - methyl] - benzaldehyde

8.85 g (20 mmol) of 4 - [N - [α - (4 - methyl - phenyl) - 2 - piperidino - benzyl] - aminocarbonylmethyl] - benzoic acid and 3.25 g (20 mmol) of N,N' - carbonyldiimidazole are refluxed in 100 ml of absolute tetrahydrofuran for 2 hours. Then the mixture is concentrated by evaporation and after the addition of 50 ml of pyridine and 3.7 g (20 mmol) of 4 - toluenesulphonic acid hydrazide, the mixture is refluxed for a further 2 hours. It is then poured on to ice water and suction filtered and the precipitate is dried. The resulting crude toluenesulphonic acid hydrazide of the carboxylic acid used is mixed with 20 g of anhydrous sodium carbonate and heated to 170°C in 50 ml of ethylene glycol for 2 hours. Then it is added to water and extracted with chloroform. The concentrated extracts are purified by column chromatography on silica gel using toluene/ethyl acetate 5:1 as eluant.
Yield: 1.73 g (21% of theory)
M.p.: 144-146°C
Calculated: C 78.84 H 7.09 N 6.57

Found: C 78.95 H 7.19 N 6.50

The following was prepared analogously to Example 6:

(a) 4-[N-[α-Phenyl-2-piperidino-benzyl]-aminocarbonyl-methyl]-benzaldehyde

Yield: 29% of theory

M.p.: 168-170°C

Calculated: C 78.61 H 6.84 N 6.79

Found: C 78.60 H 7.00 N 6.72

Example 7

4-[N-[α-(4-Methyl-phenyl)-2-piperidino-benzyl]-amino-carbonyl-methyl]-benzaldehyde

0.5 g (1.2 mmol) of 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzyl alcohol are added to a suspension of 0.4 g (1.5 mmol) of pyridinium chlorochromate in 2 ml of chloroform. After 12 hours at ambient temperature, ether is added, the mixture is filtered and the concentrated filtrate is purified by column chromatography on silica gel (eluant: toluene/ethyl acetate = 5:1).

Yield: 0.3 g (60% of theory)

M.p.: 145-146°C

Calculated: C 78.84 H 7.09 N 6.57

Found: C 78.97 H 7.12 N 6.57

The following was prepared analogously to Example 7:

(a) 4-[N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzaldehyde

Yield: 40% of theory

M.p.: 170°C

Calculated C 78.61 H 6.84 N 6.79

Found: C 78.59 H 6.87 N 6.61

Example 8

Ethyl 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonyl-methyl]-cinnamate

427 mg (1 mmol) of 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzaldehyde are added to an ethereal solution of 450 mg (2 mmol) of ethyl diethylphosphonoacetate and 100 mg (2 mmol) of 50% sodium hydride. After the mixture has been stirred overnight, water is added and the resulting mixture is extracted with chloroform and purified by column chromatography on silica gel using toluene/ethyl acetate (5:1) as eluant.

Yield: 0.18 g (36% of theory)

M.p.: 176-180°C

Calculated: C 77.39 H 7.31 N 5.64

Found: C 77.64 H 7.25 N 5.71

The following was prepared analogously to Example 8:

(a) Ethyl 4-[N-(α-phenyl-2-piperidino-benzyl)-amino-carbonylmethyl]-cinnamate

Yield: 28.6% of theory

M.p.: 159-161°C

Calculated: C 77.14 H 7.10 N 5.80

Found: C 77.28 H 7.21 N 5.65

Example 9

4-[N-[α-(4-Methyl-phenyl)-2-piperidino-benzyl]-amino-carbonyl-methyl]-cinnamic acid

Prepared by alkaline saponification of ethyl 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-amino-carbonyl-methyl]-cinnamate analogously to Example 3.

Yield: 84% of theory

M.p.: 173-176°C

Calculated: C 76.90 H 6.88 N 5.98

Found: C 77.24 H 7.01 N 5.64

The following was prepared analogously to Example 9:

(a) 4-[N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-cinnamic acid

Yield: 75% of theory

M.p.: 177-180°C

Calculated: C 76.62 H 6.65 N 6.16

Found: C 76.75 H 6.57 N 6.07

Example 10

Ethyl 4-[N-[α-(3-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate

A mixture of 0.22 g (0.8 mmol) of α-(3-methyl-phenyl-2-piperidino-benzyl alcohol and 0.15 g (0.8 mmol) of ethyl 4-cyanomethyl-benzoate in 2 ml of o-dichloro-benzene is added dropwise, at ambient temperature, to 1.5 ml of o-dichlorobenzene and 1.5 ml of concentrated sulphuric acid. After 2 hours' stirring, the mixture is poured onto ice-water, extracted once with ether, made alkaline with dilute sodium hydroxide solution and extracted with chloroform. The chloroform extract is concentrated by evaporation and the residue is recrystallised from ethanol.

Yield: 0.22 g (60% of theory)

M.p.: 158-159°C

Calculated: C 76.57 H 7.28 N 5.95

Found: C 76.41 H 7.39 N 5.76

The following was prepared analogously to Example 10:

(a) Ethyl 4-[N-[2-(3,5-cis-dimethyl-piperidino)-5-nitro-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoate

Yield: 57% of theory

M.p.: 170-173°C

Calculated: C 70.30 H 6.66 N 7.93

Found: C 70.05 H 6.68 N 7.81

Example 11

4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-amino-carbonyl-methyl]-benzoic acid

240 mg (5 mmol) of 4-[N-[5-chloro-α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid are catalytically dehalogenated in 80 ml of ethanol/dioxan (1/1) in the presence of 0.1 g of 10% palladium on charcoal at 50°C and under a hydrogen pressure of 5 bar. After cooling, the catalyst is filtered off. The filtrate is concentrated by evaporation and the residue is recrystallised from ethanol.

Yield: 0.16 g (72% of theory)

M.p.: 226-228°C

Calculated: C 75.99 H 6.83 N 6.33

Found: C 75.81 H 6.73 N 6.10

The following was prepared analogously to Example 11:

(a) 4-[N-[2-(2-methyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoic acid

From 4-[N-[5-chloro-2-(2-methyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoic acid

Yield: 68% of theory

M.p.: 246-248°C

Calculated C 75.99 H 6.83 N 6.33

Found: C 75.57 H 7.10 N 6.44

(b) 4-[N-[2-(3-Methyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoic acid

From 4-[N-[5-chloro-2-(3-methyl-piperidino)-α-phenyl-benzyl]-aminocarbonylmethyl]-benzoic acid

Calculated: 43% of theory

M.p.: 228-230°C

Calculated: C 75.99 H 6.83 N 6.33

Found: C 75.91 H 6.82 N 6.33

Example 12

Ethyl 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonyl-methyl]-benzoate

A solution of 2.78 g (10 mmol) of freshly prepared (4-methyl-phenyl)-(2-piperidinophenyl)-ketimine in 50 ml of methylenechloride is mixed with 1.5 ml (11 mmol) of triethylamine and then a solution of 2.5 g (11 mmol) of 4-ethoxycarbonyl-phenylacetic acid chloride in 20 ml of methylene chloride is added dropwise thereto, whilst the mixture is cooled with ice. After 1 hour at ambient temperature it is poured onto ice-water and extracted with methylene chloride. The extracts are dried and concentrated by evaporation and the evaporation residue is purified by column chromatography on silica gel (eluant: toluene/ethyl acetate 10:1). The crude acylimine is dissolved in dimethylformamide and, after the addition of 0.5 g of palladium (10% on charcoal), it is hydrogenated at ambient temperature under a hydrogen pressure of 5 bar. After the calculated quantity of hydrogen has been taken up the catalyst is removed by filtering, the filtrate is concentrated by evaporation and the residue is recrystallised from a little alcohol.

Yield: 2.8 g (60% of theory)

M.p.: 175-177°C

Calculated: C 76.57 H 7.28 N 5.95

Found: C 76.41 H 7.19 N 5.76

Example 13

4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonyl-methyl]-benzonitrile

Prepared from α-(4-methyl-phenyl)-2-piperidino-benzylamine and 4-cyano-phenylacetic acid analogously to Example 1.

Yield: 64% of theory

M.p.: 144-146°C

Calculated: C 79.40 H 6.90 N 9.92

Found: C 79.10 H 6.90 N 9.78

The following was prepared analogously to Example 13:

(a) 4-[N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzonitrile

Yield: 53% of theory

M.p.: 178-181°C

Calculated: C 79.18 H 6.65 N 10.26

Found: C 78.84 H 6.55 N 10.24

Example 14

Ethyl 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate

4.2 g (10 mmol) of 4-[N-[α-(4-methyl-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzonitrile are refluxed for 24 hours with 50 ml of ethanolic hydrochloric acid. The mixture is then concentrated by evaporation and the evaporation residue is mixed with aqueous sodium bicarbonate solution and extracted with chloroform. The chloroform extract is concentrated by evaporation and the residue is triturated with ethanol and suction filtered.

Yield: 2.9 g (61.6% of theory)

M.p.: 177-179°C

Calculated: C 76.57 H 7.28 N 5.95

Found: C 76.41 H 7.35 N 5.76

The following was prepared analogously to Example 14:

(a) Ethyl 4-[N-(5-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

Yield: 57% of theory

M.p.: 170-173°C

Calculated: C 76.57 H 7.28 N 5.95

Found: C 76.41 H 7.19 N 5.65

Example 15

Ethyl 4-[N-[5-chloro-α-(2-chloro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate

10 mmol of ethyl 4-[N-[α-(2-chloro-phenyl)-5-nitro-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoate are dissolved in 50 ml of dimethylformamide and, after the addition of 1 g of Raney nickel, hydrogenated at 60°C under a hydrogen pressure of 6 bar. Then the catalyst is filtered off, the filtrate is concentrated by evaporation and the residue, consisting of ethyl 4-[N-[5-amino-α-(2-chloro-phenyl)-2-piperidino-benzyl]-amino-carbonylmethyl]-benzoate is dissolved in 100 ml of concentrated hydrochloric acid. Whilst the mixture is cooled with ice, a solution of 1.0 g (14 mmol) of sodium nitrite in 10 ml of water is added dropwise thereto and the resulting mixture is stirred for 1 hour at 0 to 5°C. The reaction mixture is then added dropwise to a solution of 3 g of copper (I) chloride in 25 ml of concentrated hydrochloric acid. After 1 hour's stirring, the mixture is made alkaline with sodium hydroxide solution and extracted with chloroform. The concentrated chloroform extracts are purified by column chromatography on silica gel using toluene/ethyl acetate (5:1) as eluant.

Yield: 1.5 g (28.6% of theory)

M.p.: 213-215°C

Calculated: C 66.28 H 5.75 N 5.33 Cl 13.49

Found: C 66.40 H 5.91 N 5.41 Cl 13.40

The following was prepared analogously to Example 15

(a) Ethyl 4-[N-[5-chloro-2(3,5-cis-dimethyl-piperidino)-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoate

Yield: 28% of theory

M.p.: 188-191°C

Calculated: C 71.72 H 6.80 N 5.40 Cl 6.83

Found: C 71.95 H 6.85 N 5.35 Cl 6.77

Example 16

3-[4-[N-(α-(4-Methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid

0.91 g (2 mmol) of 4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamic acid are dissolved in 50 ml of methanol and, after the addition of 0.5 g of palladium (10% on charcoal), the mixture is catalytically hydrogenated at ambient temperature under a hydrogen pressure of 3 bar. After the hydrogen uptake has ended, the

catalyst is filtered off and recrystallised from a little acetonitrile.

Yield: 0.68 g (74% of theory)
M.p.: 146-148°C
Calculated: C 76.57 H 7.28 N 5.95
Found: C 76.41 H 7.19 N 5.61

The following was prepared analogously to Example 16:

(a) 3-[4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid
Yield: 65% of theory
M.p.: 97-99°C
Calculated: C 76.30 H 7.06 N 6.13
Found: C 76.35 H 6.95 N 5.91

Example 17

Sodium salt of 4-[N-(α-(4-methyl-phenyl)-2-piperidinobenzyl)-aminocarbonylmethyl]-benzoic acid

442 mg (1 mmol) 4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid are dissolved in 25 ml of ethanol and mixed with 1 ml of 1 N sodium hydroxide solution. The mixture is then concentrated by evaporation *in vacuo*, 20 ml of acetone are added, the precipitate obtained is suction filtered and washed with ethyl acetate.
Yield: 410 mg (85% of theory)
M.p.: 295-300°C
Calculated: C 72.40 H 6.29 N 6.03
Found: C 72.15 H 6.46 N 5.93

The following was prepared analogously to Example 17:

(a) Ethanolamine salt of 4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 75% of theory
M.p.: 188-191°C
Calculated: C 71.55 H 7.41 N 8.34
Found: C 71.16 H 7.48 N 8.52

(b) Diethanolamine salt of 4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 81% of theory
M.p.: 178-180°C
Calculated: C 70.70 H 6.86 N 7.73
Found: C 70.25 H 6.75 N 7.58

(c) Triethanolamine salt of 4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 76% of theory
M.p.: 160-165°C
Calculated: C 69.01 H 7.67 N 7.10
Found: C 68.91 H 7.64 N 7.45

(d) Ethylenediamine salt of 4-[N-(α-(4-methyl-phenyl)-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid
Yield: 65% of theory
M.p.: 160-163°C
Calculated: C 71.69 H 7.62 N 11.15
Found: C 72.04 H 7.80 N 10.96

Example 18

Ethyl 4-[N-(5-methoxy-α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoate

472 mg (1 mmol) of ethyl 4-[N-(5-hydroxy-α-phenyl-2-piperidino-benzyl)-aminocarbonmethyl]-benzoate are dissolved in 25 ml of absolute dimethylformamide. After the addition of 50 mg of 50% sodium hydride the mixture is stirred for 30 minutes. Then 0.5 g of methyl iodide are added dropwise and the resulting mixture is stirred overnight. To work it up, it is poured onto ice-water and extracted with methylene chloride. The concentrated extracts are purified by column chromatography on silica gel using toluene/ethyl acetate 4:1 as eluant.
Yield: 260 mg (53% of theory)
M.p.: 123-125°C
Calculated: C 74.05 H 7.04 N 5.76
Found: C 73.86 H 6.95 N 5.61

Example 19

Ethyl 4-[(2-methoxy-1-(2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoate

0.49 g (2.34 mmol) of 4-ethoxycarbonyl-phenylacetic acid, 0.73 g (2.78 mmol) of triphenylphosphine, 0.50 ml (3.66 mmol) of triethylamine and 0.23 ml (2.34 mmol) of carbontetrachloride are added successively to a solution of 0.55 g (2.34 mmol) of 2-methoxy-1-(2-piperidino-phenyl)-ethylamine in 5 ml of acetonitrile and the resulting mixture is stirred for 20 hours at ambient temperature. It is then concentrated by evaporation *in vacuo* and distributed between ethyl acetate and water. The organic extract is dried and filtered and evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 10/2).
Yield: 0.45 g (45% of theory)
M.p.: 122-123°C
Calculated: C 70.73 H 7.60 N 6.60
Found: C 71.04 H 7.48 N 6.39

The following was prepared analogously to Example 19:

(a) Ethyl 4-[(1-(3-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 55% of theory
M.p.: 141-143°C
Calculated: C 68.33 H 7.28 Cl 7.76 N 6.13
Found: C 68.30 H 7.16 Cl 8.03 N 6.20

(b) Ethyl 4-[(1-(6-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 73.9% of theory
M.p.: 79-82°C
Calculated: C 68.33 H 7.28 Cl 7.76 N 6.13
Found: C 68.45 H 7.24 Cl 7.80 N 6.09

(c) Ethyl 4-[(1-(4-bromo-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 62.1% of theory,
M.p.: 116-118°C
Calculated: C 62.27 H 6.63 Br 15.93 N 5.58
Found: C 62.53 H 6.48 Br 15.98 N 5.66

(d) Ethyl 4-[(1-(4-nitro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 74.6% of theory,
M.p.: 127-130°C
Calculated: C 66.79 H 7.11 N 8.99
Found: C 66.88 H 7.08 N 9.15

(e) Ethyl 4-[(1-(3-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 68% of theory,
M.p.: 145-147°C
Calculated: C 74.28 H 8.31 N 6.42
Found: C 74.40 H 8.30 N 6.41

(f) Ethyl 4-[(1-(4-methyl-2-piperidino-phenyl)-1

-butyl)-aminocarbonylmethyl]-benzoate
Yield: 54.7 of theory,
M.p.: 113-114°C
Calculated: C 74.28 H 8.31 N 6.42
Found: C 74.23 H 8.30 N 6.55
(g) Ethyl 4-[(1-(5-methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 67.9% of theory,
M.p.: 149-150°C
Calculated: C 74.28 H 8.31 N 6.42
Found: C 74.38 H 8.21 N 6.49
(h) Ethyl 4-[(1-(6-methyl-2-piperidino-phenyl-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 47% of theory,
M.p.: 92-93°C
Calculated: C 74.28 H 8.31 N 6.42
Found: C 74.50 H 8.46 N 6.48
(i) Ethyl 4-[(1-(2-pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl-benzoate
Yield: 57.3% of theory,
M.p.: 122-125°C
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.63 H 8.07 N 7.01
(k) Ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-benzoate
Yield: 71.5% of theory,
M.p.: 127-128°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.90 H 8.06 N 6.72
(l) Ethyl 4-[(1-(2-(4-methyl-piperidino)-phenyl)-1-butyl(-aminocarbonylmethyl]-benzoate
Yield: 51.1% of theory,
M.p.: 153-155°C
Calculated: C 74.28 H 8.31 N 6.42
Found: C 74.55 H 8.33 N 6.45
(m) Ethyl 4-[(1-(2-hexahydroazepino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 42.7% of theory,
M.p.: 145-147°C
Calculated: C 74.28 H 8.31 N 6.42
Found: C 73.98 H 8.26 N 6.58
(n) Ethyl 4-[(1-(5-fluoro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 55% of theory,
M.p.: 128-130°C
Calculated: C 70.88 H 7.55 N 6.36
Found: C 71.14 H 7.57 N 6.49
(o) Methyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-benzoate
Yield: 63.2% of theory,
M.p.: 147-148°C
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.66 H 7.88 N 6.80
(p) n-Butyl 4-[1-(2-piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-benzoate
Yield: 50.9% of theory,
M.p.: 117-119°C (ether)
Calculated: C 74.63 H 8.50 N 6.22
Found: C 74.49 H 8.46 N 6.14
(q) Ethyl 3-chloro-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 14.9% of theory,
M.p.: <20°C
Calculated: m/e = 456/458 (1 chloro)
Found: m/e = 456/458 (1 chloro)
(r) Ethyl 4-[(1-(2-piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoate
Yield: 18.9% of theory,
M.p.: 103-105°C
Calculated: C 74.62 H 7.89 N 6.45
Found: C 75.01 H 8.10 N 6.26
(s) Ethyl 4-[(1-(3-chloro-2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoate
Yield: 58.0% of theory,
M.p.: 166-168°C
Calculated: C 67.20 H 6.81 Cl 8.27 N 6.53
Found: C 67.17 H 6.85 Cl 8.17 N 6.45

Example 20

Ethyl 4-[(1-(5-nitro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

A solution of 14.6 g (64.6 mmol) of 4-ethoxy-carbonyl-phenyl acetic acid chloride in 20 ml of methylene chloride is added dropwise to a stirred solution of 15.1 g (54.4 mmol) of 1-(5-nitro-2-piperidino-phenyl)-1-butylamine and 8.46 ml (61.4 mmol) of triethylamine in 55 ml of dry methylene chloride within 30 minutes in such a way that the temperature does not exceed 30°C. The mixture is stirred for a further 2 hours at ambient temperature, 300 ml of methylene chloride are added and the resulting mixture is extracted twice, each time with 50 ml of water. The organic phase is dried over sodium sulphate, filtered and concentrated by evaporation in vacuo. The reddish-brown oily evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 10:1).
Yield: 17.7 g (69.7% of theory),
M.p.: 135-137°C (ether)
Calculated: C 66.79 H 7.11 N 8.99
Found: C 66.73 H 6.99 N 9.09

The following were prepared analogously to Example 20:

(a) Ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 80.20% of theory,
M.p.: 127-129°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.98 H 8.26 N 6.89
(b) Ethyl 4-[(1-(4-hydroxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 13.5% of theory,
M.p.: 178-180°C
Calculated: C 71.21 H 7.81 N 6.39
Found: C 71.27 H 7.82 N 6.40
(c) Ethyl 4-[(1-(5-hydroxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 37.4% of theory,
M.p.: 188-190°C
Calculated: C 71.21 H 7.81 N 6.39
Found: C 71.34 H 7.89 N 6.38

Example 21

4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl acetic acid

3.0 g (15.45 mmol) of p-phenylene-diacetic acid and 10 ml of thionyl chloride are refluxed for 90 minutes and then concentrated by evaporation in vacuo. The crude diacid chloride is dissolved in 100 ml of methylene chloride. Then a solution of 3.6 g (15.45 mmol) of 1-(2-piperidino-phenyl)-1-butylamine is slowly added dropwise to this solution,

with stirring, at an internal temperature of 10-15°C. after 2 hours at ambient temperature, the mixture is concentrated by evaporation in vacuo and the evaporation residue is distributed between 100 ml of ice cold 5% sodium hydroxide solution and ethyl acetate. It is filtered through kieselghur and the organic phase is separated off. The alkaline-aqueous phase is adjusted to pH 5.5 with semi-concentrated hydrochloric acid and extracted with ethyl acetate. The extract is dried over sodium sulphate and filtered and the filtrate is concentrated by evaporation in vacuo. The evaporation residue is purified by column chromatography on silica gel (chloroform/methanol = 20/1).
Yield: 0.10 g (1.6% of theory),
M.p.: 136-140°C (acetonitrile/ether)
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.17 H 8.10 N 6.85

Example 22

Ethyl 4-[(2-methyl-1-(2-methyl-1-(2-piperidino-phenyl)-1-propen-1-yl)-aminocarbonylmethyl]-benzoate

5.58 g (26.8mmol) of 4-ethyoxycarbonyl-phenylacetic acid, 8.43 g (32 mmol) of triphenylphosphine, 11.2 ml (80.4 mmol) of triethylamine and 2.6 ml (0.0268 mol) of carbon tetrachloride are successively added to a solution of 6.17 g (26.8 mmol) of freshly prepared isopropyl-(2-piperidino-phenyl)-ketimine in 62 ml of acetonitrile and the resulting mixture is stirred for 20 hours at an ambient temperature. It is then concentrated by evaporation in vacuo and distributed between ethyl acetate and water. The dried and filtered ethyl acetate extract is evaporated in vacuo. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1).
Yield: 3.0 g (26.6% of theory),
M.p.: 82-84°C (ether)
Calculated: C 74.26 H 7.67 N 6.66
Found: C 74.20 H 7.49 N 6.56

The following were prepared analogously to Example 22:

(a) Ethyl 4-[(1-2-piperidino-phenyl)-1-penten-1-yl)-aminocarbonylmethyl]-benzoate
Yield: 16% of theory,
M.p.: 94-97°C (ethanol)
Calculated°C C 74.62 H 7.89 N 6.45
Found: C 74.75 H 7.71 N 6.24

(b) Ethyl 4-[(1-2-piperidino-phenyl)-1-hexen-1-yl)-aminocarbonylmethyl]-benzoate
Yield: 27.4% of theory,
M.p.: 83-85°C (ethanol)
Calculated: C 74.97 H 8.09 N 6.24
Found: C 75.42 H 7.95 N 6.00

(c) Ethyl 4-[(1-2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoate
Yield (more lipophilic isomer; probably E form): 4.1% of theory,
M.p.: <20°C
Calculated: m/e = 420
Found: m/e = 420
Yield (less lipophilic isomer; probably Z form): 51.9% of theory,
M.p.: 115-117°C (ethanol)
Calculated: C 74.26 H 7.67 N 6.66
Found: C 73.85 H 7.59 N 6.44

(d) Ethyl 4-[(2-phenyl-1-(2-piperidino-phenyl)-ethen-1-yl)-aminocarbonylmethyl]-benzoate
Yield (more lipophilic isomer; probably E form): 4% of theory,
M.p.: 75-77°C (ether/petroleum ether)
Calculated: C 76.90 H 6.88 N 5.98
Found: C 77.31 H 7.20 N 5.93
Yield (less lipophilic isomer; probably Z form): 42.7% of theory,
M.p.: 157-160°C (ethanol)
Found: C 77.19 H 6.95 N 6.02

(e) Ethyl 4-[(3-phenyl-1-(2-piperidino-phenyl)-1-propen-1-yl)-aminocarbonylmethyl)-benzoate
Yield: 62.6% of theory,
M.p.: <20°C
Calculated: m/e = 482
Found: m/e = 482

(f) Ethyl 4-[(1-(2-(3,3-dimethyl-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoate
Yield: 33% of theory,
M.p.: 113-116°C (ethanol)
Calculated: C 74.97 H 8.09 N 6.24
Found: C 75.37 H 7.93 N 6.03

(g) Ethyl 4-[(1-(6-methyl-2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoate
Yield: 60.4% of theory (probably Z form)
M.p.: 95-96°C
Calculated: C 74.62 H 7.89 N 6.45 m/e = 434
Found: C 74.44 H 8.00 N 6.59 m/e = 434

Example 23

Ethyl 4-[(1-(2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoate

A stirred solution of 19.0 g (82.46 mmol) of freshly prepared (2-piperidino-phenyl)-propyl-ketimine and 11.5 ml (82.46 mmol) of triethylamine in 190 ml of anhydrous toluene is heated to an internal temperature of 85°C, then a solution of 18.7 g (82.46 mmol) of 4-ethoxycarbonyl-phenylacetic acid chloride in 95 ml of anhydrous toluene is added dropwise thereto within 10 minutes and the resulting mixture is stirred for 30 minutes at an internal temperature of 95°C. It is then cooled to 20°C and extracted twice with water. The organic phase is dried over sodium sulphate, filtered and concentrated by evaporation *in vacuo*. The evaporation residue is purified by repeated column chromatography (toluene/acetone = 20/1 and 50/1).
Yield: (more lipophilic isomer; probably E form): 11.2 g (23.6% of theory),
M.p: <20°C (honey-yellow viscous oil)
Calculated: C 74.26 H 7.67 N 6.66
Found: C 73.90 H 7.92 N 6.91
Yield (less lipophilic isomer; probably Z form): 15.9 g (33.5% of theory),
M.p.: 114-116°C
Found: C 74.02 H 7.69 N 6.85

Example 24

Ethyl (E)- and (Z)-4-[(1-(2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoate

1.0 g of Z ester (see Example 22c) is heated for 30 minutes in a pre-heated oil bath at 230°C. After cooling, the product obtained is purified by column chromatography on silica gel (toluene/acetone = 20/1).

Yield (E ester): 0.365 g (36.5% of theory),
M.p.: <20°C
Yield (Z ester): 0.380 g (38.0% of theory),
M.p.: 115-117°C

If the (E)-ester is heated for 3.5 hours with catalytic quantities of iodine in benzene, a 1/1 mixture of (E) and (Z) esters is obtained, according to thin layer chromatography (toluene/acetone = 10/1).

The following compounds were obtained analogously to Example 24:

(a) *Ethyl (E)- and (Z)-4-[(1-(6-methyl-2-piperidinophenyl)-1-buten-1-yl)-aminocarbonylmethyl)-benzoate*

According to thin layer chromatography, a 1/1 mixture of (E) and (Z) esters is obtained from the (Z) ester (see Example 22g).

Upper spot (E): Calculated: m/e = 434
Found: m/e = 434
lower spot (Z): Found: m/e = 434

Example 25

Ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

2.9 g (6.90 mmol) of ethyl 4-[(1-(2-piperidinophenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoate in 100 ml of ethanol is hydrogenated on 0.77 g of 10% palladium/charcoal at 50°C under a hydrogen pressure of 1 bar. After 2 hours, the catalyst is filtered off over kieselguhr and the filtrate is concentrated by evaporation *in vacuo*. The evaporation residue is crystallised from ethanol.

Yield: 1.5 g (51.5% of theory),
M.p.: 126-128°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.97 H 8.22 N 6.57

The following compounds were obtained analogously to Example 25:

(a) Ethyl 4-[(1-(2-piperidino-phenyl)-1-pentyl)-aminocarbonylmethyl]-benzoate
Yield: 45% of theory,
M.p.: 117-120°C (ether)
Calculated: C 74.28 H 8.31 N 6.42
Found: C 74.60 H 8.13 N 6.27

(b) Ethyl 4-[(1-(2-piperidino-phenyl)-1-hexyl)-aminocarbonylmethyl]-benzoate
Yield: 50% of theory,
M.p.: 108-110°C (ether)
Calculated: C 74.63 H 8.50 N 6.22
Found C 74.85 H 8.33 N 6.01

(c) Ethyl 4-[(2-phenyl-1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoate
Yield: 87.6% of theory,
M.p.: 161-162°C (ethanol)
Calculated: C 76.57 H 7.28 N 5.95
Found: C 76.71 H 7.19 N 5.99

(d) Ethyl 4-[(3-phenyl-1-(2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoate
Yield: 57.6% of theory,
M.p.: 118-119°C (ethanol)
Calculated: C 76.83 H 7.49 N 5.78
Found: C 76.70 H 7.49 N 5.90

(e) Ethyl 4-[(1-(2-(3,3-dimethyl-piperidino)-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 36.5% of theory,
M.p.: 140-141°C (ethanol)
Calculated: C 74.63 H 8.50 N 6.22
Found: C 74.30 H 8.23 N 6.12

Example 26

4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

A mixture of 1.2 g (2.84 mmol) of ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate and 4.26 ml of 1N sodium hydroxide solution in 12 ml of ethanol is stirred for 1 hour at 60°C, then neutralised with 4.26 ml of 1N hydrochloric acid and the ethanol is evaporated off *in vacuo*. The residue is distributed between ethyl acetate and water; the organic extract is dried and filtered and concentrated by evaporation *in vacuo*. The evaporation residue is crystallised from ethanol.

Yield: 0.50 g (44.6% of theory),
M.p.: 213-215°C
Calculated: C 73.07 H 7.66 N 7.10
Found: C 73.18 H 7.51 N 7.10

The following compounds were obtained analogously to Example 26:

(a) 4-[(1-(2-piperidino-phenyl)-1-pentyl)-aminocarbonylmethyl]-benzoic acid
Yield: 70.2% of theory,
M.p.: 213-215°C (acetone)
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.71 H 7.70 N 6.90

(b) 4-[(1-(2-piperidino-phenyl)-1-hexyl)-aminocarbonylmethyl]-benzoic acid
Yield: 72.6% of theory,
M.p.: 197-200°C (acetone)
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.83 H 7.93 N 6.77

(c) 4-[(2-phenyl-1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid
Yield: 68.7% of theory,
M.p.: 214-215°C (acetone)
Calculated: C 75.99 H 6.83 N 6.33
Found: C 75.70 H 6.60 N 6.32

(d) 4-[(3-Phenyl-1-(2-piperidino-phenyl)-1-propyl)-aminocarbonylmethyl]-benzoic acid
Yield: 67.7% of theory,
M.p.: 167-170°C (ethyl acetate)
Calculated: C 76.29 H 7.06 N 6.14
Found: C 76.56 H 7.06 N 6.23

(e) 4-[2-Methoxy-1-(2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid
Yield: 60.8% of theory,
M.p.: 196-198°C (ether)
Calculated: C 69.68 H 7.12 N 7.07
Found: C 69.72 H 6.52 N 6.71

(f) 4-[(1-(2-Piperidino-phenyl)-4-penten-1-yl)-aminocarbonylmethyl]-benzoic acid x 0.67 H_2O
Yield: 30.7% of theory,
M.p.: 193-197°C (ether/petroleum ether)
Calculated: C 71.74 H 7.38 N 6.69
Found: C 71.63 H 7.21 N 6.34

(g) 4-[(1-(2-(3,3-Dimethyl-piperidino)-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 48.2% of theory,
M.p.: 168-170°C (petroleum ether)
Calculated: C 73.91 H 8.11 N 6.63
Found: C 73.51 H 7.89 N 6.32

(h) 4-[(1-(3-Methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 53% of theory,

M.p.: 179-182°C
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.50 H 7.82 N 7.01

(i) 4-[(1-(4-Methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 85.6% of theory,
M.p.: 170-172°C
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.25 H 7.64 N 6.89

(k) 4-[(1-(5-Methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 62.1% of theory,
M.p.: 219-221°C
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.20 H 7.74 N 6.89

(l) 4-[(1-(6-Methyl-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid × 0.3 H_2O
Yield: 89% of theory,
M.p.: 158-160°C
Calculated: C 72.53 H 7.93 N 6.77
Found: C 72.40 H 7.91 N 6.92

(m) 4-[(1-(3-Chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 70% of theory,
M.p.: 189-191°C
Calculated: C 67.20 H 6.81 Cl 8.27 N 6.53
Found: C 67.30 H 6.85 Cl 8.36 N 6.58

(n) 4-[(1-(4-Chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 57.8% of theory,
M.p.: 188-189°C
Calculated: C 67.20 H 6.81 Cl 8.27 N 6.53
Found: C 66.90 H 7.00 Cl 8.22 N 6.53

(o) 4-[(1-(5-Chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 81.6% of theory,
M.p.: 226-229°C
Calculated: C 67.20 H 6.81 Cl 8.27 N 6.53
Found: C 67.17 H 6.59 Cl 8.51 N 6.60

(p) 4-[(1-(6-Chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 69.4% of theory,
M.p.: 150-153°C
Calculated: C 67.20 H 6.81 Cl 8.27 N 6.53
Found: C 67.18 H 6.91 Cl 8.42 N 6.77

(q) 4-[(1-(4-Bromo-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 84.4% of theory,
M.p.: 198-201°C
Calculated: C 60.89 H 6.17 Br 16.88 N 5.92
Found: C 60.88 H 5.98 Br 17.20 N 5.98

(r) 4-[(1-(5-Bromo-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 90.7% of theory,
M.p.: 232-235°C
Calculated: C 60.89 H 6.17 Br 16.88 N 5.92
Found: C 60.96 H 6.13 Br 16.85 N 5.90

(s) 4-[(1-(4-Nitro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 70.9% of theory,
M.p.: 188-190°C
Calculated: C 65.59 H 6.65 N 9.56
Found: C 65.30 H 6.44 N 9.53

(t) 4-[(1-(5-Nitro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 90.7% of theory,
M.p.: 225-227°C
Calculated: C 65.59 H 6.65 N 9.56
Found: C 65.80 H 6.61 N 9.72

(u) 4-[(1-(4-Hydroxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid × 0.5 H_2O
Yield: 95.7% of theory,
M.p.: softening from 70°C (foam)
Calculated: (× 0.5 H_2O) C 68.71 H 7.45 N 6.68
Found C 68.63 H 7.55 N 6.26

(v) 4-[(1-(5-Hydroxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 89.3% of theory,
M.p.: 186-190°C
Calculated: C 70.22 H 7.37 N 6.82
Found: C 70.31 H 7.58 N 6.51

(w) 4-[(1-(4-Methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 78.6% of theory,
M.p.: 185-187°C
Calculated: C 70.73 H 7.60 N 6.60
Found: C 70.46 H 7.77 N 6.56

(x) 4-[(1-(5-Methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 75% of theory,
M.p.: 182-185°C (decomp.)
Calculated: C 70.73 H 7.60 N 6.60
Found: C 70.52 H 7.50 N 6.70

(y) 4-[(1-(2-Pyrrolidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 64.5% of theory,
M.p.: 200-203°C
Calculated: C 72.61 H 7.42 N 7.36
Found: C 72.64 H 7.50 N 7.38

(z) 4-[(1-(2-(4-Methyl-piperidino)-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 81.4% of theory,
M.p.: 197-201°C
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.90 H 8.06 N 7.00

(aa) 4-[(1-(2-Hexahydroazepino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 65.6% of theory,
M.p.: 199-202°C
Calculated: C 73.50 H 7.90 N 6.86
Found: C 73.50 H 7.90 N 6.76

(ab) 4-[(1-(4-Fluoro-2 piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 87.1% of theory,
M.p.: 204-207°C
Calculated: C 69.88 H 7.09 N 6.79
Found: C 70.25 H 7.02 N 7.12

(ac) 4-[(1-(5-Fluoro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 53.9% of theory,
M.p.: 200-202°C
Calculated: C 69.88 H 7.09 N 6.79
Found: C 69.67 H 7.24 N 6.90

(ad) 3-Chloro-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 51% of theory,
M.p.: 165-168°C
Calculated: C 67.20 H 6.81 N 6.53 m/e = 428/430 (1

chlorine)
Found: C 66.92 H 6.69 N 6.55 m/e = 428/430 (1 chlorine)
(ae) 4-[(1-(3-Methyl-2-piperidino-phenyl)-1-ethyl)-aminocarbonylmethyl]-benzoic acid
Yield: 79% of theory,
M.p.: 230-231°C
Calculated: C 72.60 H 7.42 N 7.36
Found: C 72.75 H 7.58 N 7.30
(af) 4-[(1-(3-Chloro-2-piperidino-phenyl)-1-ethyl-aminocarbonylmethyl]-benzoic acid
Yield: 54% of theory,
M.p.: 192-195°C (75% aqueous ethanol)
Calculated: C 65.91 H 6.28 Cl 8.84 N 6.99
Found: C 66.00 H 6.44 Cl 8.67 N 6.78

Example 27

4-[(2-Methyl-1-(2-piperidino-phenyl)-1-propen-1-yl)-aminocarbonylmethyl]-benzoic acid

A mixture of 3.5 g (8.3 mmol) of ethyl 4-[(2-methyl-1-(2-piperidino-phenyl)-1-propen-1-yl)-aminocarbonylmethyl] benzoate and 12.5 ml of 1N sodium hydroxide solution in 95 ml of ethanol is stirred at 60°C for 2 hours. It is neutralised with 12.5 ml of 1N hydrochloric acid, concentrated by evaporation *in vacuo* and distributed between ethyl acetate and water. The dried, filtered organic extract is evaporated *in vacuo*. The evaporation residue is crystallised from ethanol.
Yield: 2.4 g (73.6% of theory),
M.p.: 188-191°C
Calculated: C 73.44 H 7.19 N 7.14
Found: C 73.60 H 7.19 N 7.02

The following compounds were obtained analogously to Example 27:

(a) (E)-4-[(1-(2-Piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid
Yield: 71.5% of theory,
M.p.: 188-190°C
Calculated: C 73.44 H 7.19 N 7.14
Found: 73.15 H 7.13 N 7.10
Olefinic proton: ^{1}H-NMR ($CDCl_3$): $\delta = 6.42$ ppm
(b) (Z)-4-[(1-(2-Piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid
Yield: 57.8% of theory,
M.p.: 174-175°C (ethanol)
Calculated: C 73.44 H 7.19 N 7.14
Found: C 73.54 H 6.97 N 7.17
Olefinic proton: ^{1}H-NMR ($CDCl_3$): $\delta = 5.60$ ppm
(c) (E)-4-[(2-Phenyl-1-(2-piperidino-phenyl)-ethen-1-yl)-aminocarbonylmethyl]-benzoic acid × 0.4 H_2O
Yield: 33.2% of theory,
M.p.: 165-167°C (ether/petroleum ether)
Calculated: (× 0.4 H_2O) C 75.11 H 6.48 N 6.26
Found: C 75.22 H 6.39 N 6.26
olefinic proton: ^{1}H-NMR ($CDCl_3$): $\delta > 6.9$ ppm
(d) (Z)-4-[(2-Phenyl-1-(2-piperidino-phenyl)-ethen-1-yl)-aminocarbonylmethyl]-benzoic acid × 1 H_2O
Yield: 72% of theory,
M.p.: 182-185°C (methanol)
Calculated: (× 1 H_2O): C 73.34 H 6.60 N 6.11
Found: C 73.55 H 6.45 N 6.00
olefinic proton: ^{1}H-NMR ($CDCl_3$): $\delta = 6.50$ ppm
(e) 4-[(3-Phenyl-1-(2-piperidino-phenyl)-1-propen-1-yl)-aminocarbonylmethyl]-benzoic acid
Yield: 48.3% of theory,
M.p.: 162-164°C (ether); probably (Z) form
Calculated: C 76.63 H 6.65 N 6.16
Found: C 76.30 H 6.47 N 6.31
Olefinic proton: ^{1}H-NMR ($CDCl_3$): $\delta = 5.80$ ppm
(f) 4-[(1-(2-(3,3-Dimethyl-piperidino)-phenyl-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid
Yield: 64.1% of theory,
M.p.: 152-153°C (ethyl acetate); probably (Z) form
Calculated: C 74.26 H 7.67 N 6.67
Found: C 73.93 H 7.57 N 6.50
Olefinic proton: ^{1}H-NMR ($CDCl_3$): $\delta = 5.55$ ppm
(g) (Z)-4-[(1-(6-Methyl-2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid
Yield: 53.3% of theory,
M.p.: 142-145°C
Calculated: C 73.66 H 7.44 N 6.89
Found: C 73.56 H 7.73 N 7.15
olefinic proton: ^{1}H-NMR ($CDCl_3$): $\delta = 5.38$ ppm

Example 28

4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

200 mg (0.51 mmol) of 4-[(1-(2-piperidino-phenyl)-1-buten-1-yl)-aminocarbonylmethyl]-benzoic acid in 10 ml of absolute ethanol are hydrogenated over 100 mg of palladium/charcoal (10%) at 50°C and under 1 bar of hydrogen, with shaking. After 1.5 hours the mixture is filtered and concentrated by evaporation *in vacuo*.
Yield: 68% of theory,
M.p.: 213-214°C
Calculated: C 73.07 H 7.66 N 7.10
Found: C 73.21 H 7.82 N 7.02
The yield is 56% of theory if hydrogenation is carried out at 50°C and under 1 bar of hydrogen on Raney nickel.

Example 29

Sodium salt of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid × 0.5 H_2O

10.0 g (25.35 mmol) of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid are dissolved at 50°C in 2000 ml of ethanol and 25.35 ml of 1N sodium hydroxide solution are added thereto. The mixture is evaporated to dryness *in vacuo* and the evaporation residue is dissolved in the minimum amount of ethanol, whilst being heated over a steam bath. The solution is cooled in an ice bath, the crystals precipitated are filtered off and washed with ether and dried at 140°C/15 torr.
Yield: 9 g (85.3% of theory),
M.p.: 280-285°C (decomp.); softening from 255°C
Calculated: (× 0.5 H_2O) C 67.74 H 6.87 N 6.58
Found: C 67.86 H 7.13 N 6.49

Example 30

Ethyl (+)-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

To a stirred solution of 2.58 g (11.1 mmol) of (+)-1-(2-piperidino-phenyl)-1-butylamine [$Bp_{0.03}$: 87°C; ee = 86 (HPLC, after derivatising with (+)-1-phenethyl-isocyanate)] in 26 ml of acetonitrile, there are added, at 20°C, one after another, 2.31 g (11.1 mmol) of 4-ethoxycarbonyl-phenyl acetic acid, 3.50 g (13.3 mmol) of triphenylphosphine, 4.60 ml (33.9

mmol) of triethylamine and 1.03 ml (11.1 mmol) of carbon tetrachloride. After 14 hours at 20°C and 1.5 hours at 40°C the mixture is concentrated by evaporation *in vacuo* and distributed between water and ether. The organic phase is dried over sodium sulphate, then filtered, and concentrated by evaporation *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 6:1).

Yield: 2.63 g (56% of theory),
M.p.: 118-120°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 74.02 H 7.97 N 6.51
$[\alpha]_D^{20} = +9.2°$ (c = 1; methanol)

The following compound was obtained analogously to Example 30:

(a) Ethyl (−)-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Prepared from (−)-1-(2-Piperidino-phenyl)-1-butylamine × 1.4 HCl [$[\alpha]_D^{20} = -20.0°$ (c = 1, methanol),
Melting range: 90-100°C; ee = 80 (HPLC, after derivatising the base with (+)-1-phenethyl-isocyanate)]
Yield: 52.6% of theory,
M.p.: 115-120°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.83 H 8.01 N 6.47
$[\alpha]_D^{20} = -9.0°$ (c = 1, methanol)

Example 31

Ethyl (+)-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

1.0 g (3.27 mmol) of (+0-1-(2-piperidino-phenyl)-1-butylamine-dihydrochloride [$[\alpha]_D^{20} = +18.7°$ (c = 1, methanol); m.p.: decomposition from 115°C; ee = 91.6 (HPLC, after derivatising the base with (+)-1-phenethyl-isocyanate)] is suspended in 6 ml of methylene chloride, then 1.4 ml (10 mmol) of triethylamine are added, with stirring, and then the solution of 0.82 g (3.64 mmol) of 4-ethoxycarbonyl-phenylacetic acid chloride in 2.4 ml of methylene chloride is added dropwise thereto, whereupon the reaction temperature rises from 22°C to 38°C. The mixture is stirred for 6 hours at ambient temperature and then extracted successively:
twice with 10 ml of water,
once with 10 ml of 2N hydrochloric acid and
once with 10 ml of water.
The organic phase is dried over sodium sulphate, filtered and concentrated by evaporation *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 6/1).
Yield: 0.53 g (38.2% of theory),
M.p.: 120-122°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.96 H 7.98 N 6.61
$[\alpha]_D^{20} = +9.0°$ (c = 1, methanol)

Example 32

(+)-4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

2.0 g (4.73 mmol) of ethyl (+)-4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate [$[\alpha]_D^{20} = +9.2°$ (c = 1, methanol)] in 20 ml of ethanol are stirred with 7.0 ml of 1N sodium hydroxide solution for 2.5 hours in a bath at 65°C. The mixture is cooled and 7.0 ml of 1N hydrochloric acid are added. The crystals which are slowly precipitated are filtered off, washed with water and dried at 100°C/4 torr.
Yield: 1.65 g (88.2% of theory),
M.p.: 185-187°C
Calculated: C 73.07 H 7.66 N 7.10
Found: C 72.90 H 7.80 N 7.17
$[\alpha]_D^{20} = +7.9°$ (c = 1, methanol)

The following compound was obtained analogously to Example 32:

(a) (−)-4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid.
Yield: 80% of theory,
M.p.: 187-190°C
Calculated: C 73.07 H 7.66 N 7.10
Found: C 72.98 H 7.44 N 7.22
$[\alpha]_D^{20} = -7.9°$ (c = 1, methanol)

Example 33

4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzonitrile

Prepared from 1-(2-piperidino-phenyl)-1-butylamine and 4-cyano-phenylacetic acid analogously to Example 19.
Yield: 57.3% of theory,
M.p.: 147-148°C
Calculated: C 76.76 H 7.78 N 11.19
Found: C 76.46 H 7.81 N 11.10

The following compound was obtained analogously to Example 33:

(a) 4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-toluene
Prepared with 4-tolyl-acetic acid.
Yield: 60.4% of theory,
M.p.: 150-153°C
Calculated: C 79.08 H 8.85 N 7.68
Found: C 78.97 H 8.58 N 7.77

Example 34

Ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared from 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzonitrile with ethanolic hydrochloric acid analogously to Example 14.
Yield: 58% of theory,
M.p.: 127-128°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 74.07 H 8.23 N 6.87

Example 35

Ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

Prepared analogously to Example 10 from 1-(2-piperidino-phenyl)-1-butanol and ethyl 4-cyanomethylbenzoate with concentrated sulphuric acid in o-dichlorobenzene at ambient temperature.
Yield: 21% of theory,
M.p.: 126-128°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 74.12 H 8.20 N 6.45

The following compound was obtained analogously to Example 35:

(a) 4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Prepared from 1-(2-piperidino-phenyl)-1-butanol

and 4-cyanomethyl-benzoic acid. Extraction at pH 5.5.
Yield: 29% of theory,
M.p.: 215-217°C
Calculated: C 73.07 H 7.66 N 7.10
Found: C 72.82 H 7.69 N 6.95

Example 36

4-[(1-(4-Amino-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid x 0.5 H_2O

0.60 g (1.365 mmol) of 4-[(1-(4-nitro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid in 10 ml of dimethylformamide are hydrogenated on 0.1 g of 10% palladium/charcoal for 3 hours at 25°C and under a hydrogen pressure of 1 bar. The catalyst is filtered off using kieselguhr and the filtrate is concentrated by evaporation *in vacuo*. The evaporation residue is crystallised from ether.
Yield: 0.41 g (73.2% of theory),
M.p.: 118-120°C
Calculated: (x 0.5 H_2O): C 68.87 H 7.71 N 10.04
Found: C 68.62 H 7.64 N 10.08

The following compounds were obtained analogously to Example 36:

(a) Ethyl 4-[(1-(4-amino-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 81.7% of theory,
M.p.: 145-146°C (ether/petroleum ether)
Calculated: C 71.37 H 8.06 N 9.60
Found: C 71.50 H 8.08 N 9.68

(b) 4-[(1-(5-Amino-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid
Yield: 64% of theory,
M.p.: 227-230°C
Calculated: C 70.39 H 7.63 N 10.26
Found: C 70.54 H 7.54 N 10.36

(c) Ethyl 4-[(1-(5-amino-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 84.3% of theory,
M.p.: 162-165°C
Calculated: C 71.37 H 8.06 N 9.60
Found: C 71.58 H 7.83 N 9.65

Example 37

Ethyl 4-[(1-(5-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

A cold diazonium salt solution (0°C) is prepared from 2.0 g (4.57 mmol) of ethyl 4-[(1-(5-amino-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate in 4.8 ml of semiconcentrated hydrochloric acid and 0.315 g (4.57 mmol) of sodium nitrite in 1.66 ml of water. This solution is added dropwise, at 0 to 5°C, to a stirred mixture of 0.59 g (5.94 mmol) of copper (I) chloride and 2.4 ml of conc. hydrochloric acid and the resulting mixture is then heated in a bath at 50°C. After the development of gas has ended (about 15 minutes), the mixture is cooled, added to ice/conc. ammonia and extracted four times, each time with 100 ml of ethyl acetate. The combined organic extracts are shaken with water, dried and filtered and evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/ethyl acetate = 10/1.
Yield: 0.80 g (40% of theory),
M.p.: 137-140°C (ether)
Calculated: C68.32 H 7.27 Cl 7.75 N 6.13
Found: C 68.42 H 7.09 Cl 8.06 N 6.05

The following compounds were obtained analogously to Example 37:

(a) Ethyl 4-[(1-(4-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 21.9% of theory,
M.p.: 123-125°C
Calculated: C 68.32 H 7.27 Cl 7.75 N 6.13
Found: C 68.70 H 7.18 Cl 7.77 N 6.08

(b) Ethyl 4-[(1-(5-bromo-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 53.8% of theory,
M.p.: 140-142°C
Calculated: C 62.27 H 6.63 Br 15.93 N 5.58
Found: C 62.39 H 6.78 Br 15.85 N 5.59

(c) Ethyl 4-[(1-(4-fluoro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 21.6% of theory,
M.p.: 110-112°C
Calculated: C 70.88 H 7.55 N 6.36
Found: C 71.01 H 7.53 N 6.21
In addition, 40% of ethyl 4-[(1-(4-hydroxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate are isolated (solid foam).

(d) Ethyl 4-[(1-(5-fluoro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 2% of theory,
M.p.: 127-129°C
Calculated: m/e = 440
Found: m/e = 440

(e) 4-[(1-(4-Fluoro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid
Yield: 16.9% of theory,
M.p.: 172-175°C
Calculated: C 68.73 H 6.55 N 7.29
Found: C 68.78 H 6.62 N 7.31

Example 38

4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

1.0 g (2.33 mmol) of 4-[(1-(5-chloro-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid in 40 ml of absolute ethanol are hydrogenated on 0.5 g of 10% palladium/charcoal at 50°C and under 5 bar of hydrogen. After 2 hours, the catalyst is filtered off over kieselguhr and the filtrate is concentrated by evaporation *in vacuo*. The evaporation residue is distributed at pH 6 between water and ethyl acetate. The organic extract is washed with water, dried and filtered and evaporated *in vacuo*.
Yield: 0.61 g (66% of theory),
M.p.: 213-215°C
Calculated: C 73.07 H 7.66 N 7.10
Found: C 73.18 H 7.42 N 7.27
The same compound is also obtained from the corresponding 4-chlorine-, 3-chlorine- or 6-chlorine-substituted starting products.

Example 39

Ethyl 4-[(1-(4-Methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

A solution of 5.0 g (11.4 mmol) of ethyl 4-[(1-(4-hydroxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate in 45 ml of absolute dimethylformamide is added dropwise, with stirring, at ambient temperature, to 548 mg (11.4 mmol) of sodium hydride (50% in oil) in 10 ml of absolute dimethylformamide. The mixture is stirred

for a further 15 minutes and then a solution of 0.71 ml (11.4 mmol) of methyliodide in 8 ml of absolute dimethylformamide is slowly added dropwise thereto. The mixture is stirred for a further 2.5 hours at ambient temperature, evaporated *in vacuo* and distributed between water and ether. The ether phase is dried and filtered and concentrated by evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 20/1).
Yield: 1.8 g (34.9% of theory),
M.p.: 115-117°C
Calculated: C 71.65 H 8.02 N 6.19
Found: C 71.47 H 7.86 N 6.19

The following compound was obtained analogously to Example 39:

(a) Ethyl 4-[(1-(5-methoxy-2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 68.4% of theory,
M.p.: 142-145°C
Calculated: C 71.65 H 8.02 N 6.19
Found: C 71.87 H 8.06 N 6.38

Example 40

2,3-Dihydroxy-propyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

A solution of 2.0 g (5.07 mmol) of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid and 0.85 g (5.27 mmol) of N,N'-carbonyldiimidazole in 20 ml of absolute tetrahydrofuran is refluxed for 1 hour, then 3.7 ml (50.7 mmol) of glycerol are added and the resulting mixture is refluxed for a further 15 hours. It is then concentrated by evaporation *in vacuo*, distributed between water and ethyl acetate, the organic solution is dried and filtered and evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 1:1).
Yield: 1.1 g (46.2% of theory),
M.p.: 120-122°C
Calculated: C 69.21 H 7.74 N 5.98
Found: C 69.23 H 7.78 N 5.93

The following compounds were obtained analogously to Example 40:

(a) 2-hydroxy-ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 80% of theory,
M.p.: 125-127°C
Calculated: C 71.21 H 7.81 N 6.39
Found: C 71.35 H 7.54 N 6.33

(b) 2-methoxy-ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate
Yield: 55.9% of theory,
M.p.: 120-123°C
Calculated: C 71.65 H 8.02 N 6.19
Found: C 72.03 H 8.03 N 6.24

Example 41

2-nicotinoyloxy-ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate

A solution of 0.7 g (4.68 mmol) of nicotinic acid chloride in 20 ml of methylene chloride is rapidly added dropwise to a stirred solution of 2.0 g (4.56 mmol) of 2-hydroxyethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate in 40 ml of methylene chloride and 0.7 ml (4.81 mmol) of triethylamine. The resulting mixture is stirred at 20°C for 2.5 hours, extracted with water, then the organic phase is dried and filtered and evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 5/1).
Yield: 1.1 g (44% of theory),
M.p.: 132-135°C
Calculated: C 70-70 H 6.86 N 7.73
Found: C 70.82 H 6.82 N 7.91

Example 42

4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzyl alcohol

A solution of 5.0 g (11.83 mmol) of ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoate in 75 ml of absolute tetrahydrofuran is added dropwise, at an internal temperature of 0°C, to a stirred suspension of 0.68 g (17.95 mmol) of lithium aluminium hydride in 25 ml of absolute tetrahydrofuran. The mixture is stirred for 20 hours at ambient temperature then cooled to 0°C and 4N sodium hydroxide solution is slowly added dropwise thereto until a filterable precipitate has formed. The mixture is filtered and the precipitate is decocted several times with ether. The combined organic solutions are concentrated by evaporation *in vacuo*. The evaporation residue is distributed between water and ether. The ether phase is dried and filtered and concentrated by evaporation *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 5/1).
Yield: 1.0 g (22% of theory),
M.p.: 152-154°C
Calculated: C 75.75 H 8.48 N 7.36
Found: C 75.90 H 8.45 N 7.28

Example 43

4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzaldehyde

6.6 g (62 mmol) of sodium carbonate are heated together with 62 ml of ethylene glycol in a bath at 170°C and, within 1 minute, 6.2 g (11 mmol) of N^1-[4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl-methyl]-benzoyl]-N^2-tosyl-hydrazine (melting point 195°C (decomposition)) are added thereto, with rapid stirring, whereupon there is a vigorous development of gas. The mixture is then heated for a further 2.5 minutes at 170°C and then immediately poured onto ice. It is extracted with ether and the ether solution is dried, filtered and concentrated by evaporation *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (chloroform/acetone = 20/1).
Yield: 2.2 g (52.9% of theory),
M.p.: 142-145°C
Calculated: C 76.16 H 7.99 N 7.40
Found: C 76.26 H 7.96 N 7.37

Example 44

Ethyl 4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamate

A solution of 2.80 g (12.5 mmol) of ethyl diethylphosphonoacetate in 10 ml of absolute dimethylformamide is added dropwise, at ambient temperature, to 0.60 g (12.5 mmol) of sodium hydride (50% in oil) in 15 ml of absolute dimethylformamide. The mixture is stirred for 15 minutes (until the development of gas ceases) and then a solution of 2.4 g (6.34 mmol) of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocar-

bonylmethyl] - benzaldehyde in 10 ml of absolute dimethylformamide is added dropwise thereto. The mixture is stirred for 2 hours at ambient temperature, concentrated by evaporation *in vacuo* and distributed between water and ether. The ether phase is dried and filtered and then evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (toluene/acetone = 10/1).

Yield: 0.85 g (29.9% of theory),
M.p.: 135-137°C (ether/petroleum ether)
Calculated: C 74.97 H 8.09 N 6.24
Found: C 74.91 H 7.89 N 6.29

Example 45

4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamic acid

Prepared by alkaline saponification of ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamate analogously to Example 26.

Yield: 64% of theory,
M.p.: 180-183°C
Calculated: C 74.26 H 7.67 N 6.66
Found: C 74.03 H 7.47 N 6.80

Example 46

Ethyl 3-[4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionate

0.60 g (1.34 mmol) of ethyl 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-cinnamate are hydrogenated in 10 ml of ethanol on 0.20 g of 10% palladium/charcoal at ambient temperature under 5 bar of hydrogen. The mixture is filtered and concentrated by evaporation *in vacuo*.

Yield: 0.53 g (88% of theory),
M.p.: 98-99°C (petroleum ether)
Calculated: C 74.63 H 8.50 N 6.22
Found: C 74.64 H 8.58 N 6.23

The following compound was obtained analogously to Example 46:

(a) 3-[4-[(1-(2-Piperidino-phenyl)-1-butyl)-amino-carbonylmethyl]-phenyl]-propionic acid

Yield: 63% of theory,
M.p.: 131-133°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.96 H 8.30 N 6.56

Example 47

3-[4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-phenyl]-propionic acid

Prepared by alkaline saponification of ethyl 3-[4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonyl-methyl]-phenyl]-propionate analogously to Example 26.

Yield: 50% of theory,
M.p.: 131-133°C
Calculated: C 73.90 H 8.11 N 6.63
Found: C 73.82 H 8.07 N 6.41

Example 48

Ethyl 4-[(α-aminocarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

At 20°C, 0.90 g (5.5 mmol) of N,N'-carbonyldi-imidazole are added to a stirred solution of 2.0 g (4.7 mmol) of ethyl 4-[(α-carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate x 0.167 H_2O (melting point 156-159°C) in 20 ml of anhydrous tetrahydrofuran and the mixture is then heated for half an hour in a bath at 80°C. The mixture is than cooled to 60°C and at this temperature a vigorous current of dry ammonia is introduced over a period of half an hour. Then the resulting mixture is evaporated *in vacuo*, distributed between water and chloroform, then the combined chloroform extracts are shaken with a little water, dried, filtered and evaporated *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (chloroform/methanol = 5/1).

Yield: 1.0 g (50.2% of theory),
M.p.: 160-162°C (acetone)
Calculated: C 68.07 H 6.90 N 9.92
Found: C 68.40 H 6.92 N 9.84

Example 49

Ethyl 4-[(α-cyano-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate

234 mg (1.22 mmol) of 4-toluenesulphochloride are added in two batches to 520 mg (1.22 mmol) of ethyl 4-[(α-aminocarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 0.22 ml of pyridine and the mixture is heated to 50°C. After 2 hours and then 1 hour later, the same quantities of pyridine and 4-toluenesulphochloride are again added and the resulting mixture is heated for a further hour at 50°C. After it has been left to stand for 2 days at 20°C, 2N ammonia is added and the mixture is extracted with chloroform. The chloroform solution is extracted twice with water. After drying and filtering, it concentrated by evaporation *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (chloroform/methanol = 10/1).

Yield: 325 mg (65.7% of theory),
M.p.: 114-117°C (ether/petroleum ether)
Calculated: C 71.09 H 6.71 N 10.36
Found: C 70.79 H 6.56 N 10.10

Example 50

4-[(α-Cyano-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid

1.5 g (3.7 mmol) of ethyl 4-[(α-cyano-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoate in 15 ml of dioxan are stirred together with 3.7 ml of 1N sodium hydroxide solution for 45 minutes in a bath at 60°C and for a further 45 minutes in a bath at 80°C. After cooling with ice, the mixture is combined with 3.7 ml of 1N hydrochloric acid, the dioxan is evaporated off *in vacuo* and the residue is distributed between water and chloroform. The organic solution is extracted with a little water, then dried and filtered and concentrated by evaporation *in vacuo*. The evaporation residue is purified by column chromatography on silica gel (chloroform/ethanol = 5/1).

Yield: 0.50 g (35.7% of theory),
M.p.: 176-180°C (decomposition)
Calculated: C 70.01 H 6.14 N 11.13
Found: C 70.02 H 6.19 N 11.05

Example 51

4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid x H_2SO_4

5 ml (2.50 mmol) of 1N sulphuric acid are added to a solution of 1.0 g (2.53 mmol) of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid in 50 ml of ethanol, the mixture is concentrated to dryness *in vacuo* and triturated with acetone.

Yield: 0.80 g (65% of theory),
M.p.: 192-197°C (decomposition).
Calculated: C 58.53 H 6.55 N 5.69 S 6.49

Found: C 58.05 H 6.54 N 5.49 S 6.35

The following addition salt was obtained analogously to Example 51:

(a) *4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid x 0.5 H_2SO_4 x 1.5 H_2O*

Prepared analogously to Example 51 with half the quantity of sulphuric acid.

Yield: 59.3% of theory,

M.p.: 180-185°C decomposition at 207-210°C

Calculated C 61.26 H 7.28 N 5.95 S 3.40

Found: C 61.28 H 6.99 N 6.10 S 3.23

Example A

Tablets containing 5 mg of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Composition:

1 tablet contains:

Active substance	(1)	5.0 mg
Corn starch	(2)	62.0 mg
Lactose	(3)	48.0 mg
Polyvinylpyrrolidone	(4)	4.0 mg
Magnesium stearate	(5)	1.0 mg
		120.0 mg

Method of preparation:

1, 2, 3 and 4 are mixed together and moistened with water. The moist mixture is pressed through a screen with a mesh width of 1.5 mm and dried at about 45°C. The dry granulate is passed through a screen with a mesh width of 1.0 mm and mixed with 5. The finished mixture is compressed in a tablet press, using punches 7 mm in diameter provided with a dividing slot, to form tablets.

Weight of tablet: 120 mg

Example B

Coated tablets containing 2.5 mg of 4-[(1-(2 piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

1 tablet core contains:

Active substance	(1)	2.5 mg
Potato starch	(2)	44.0 mg
Lactose	(3)	30.0 mg
Polyvinylpyrrolidone	(4)	3.0 mg
Magnesium stearate	(5)	0.5 mg
		80.0 mg

Method of preparation:

1, 2, 3 and 4 are thoroughly mixed and moistened with water. The moist mass is passed through a screen with a mesh width of 1 mm, then dried at 45°C and the granulate is again passed through the same screen. After the addition of 5, convex tablet cores 6 mm in diameter are produced in a tablet-making machine by compression. The tablet cores thus produced are coated in known manner with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

Weight of coated tablet: 120 mg

Example C

Tablets containing 10 mg of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

Composition:

1 tablet contains:

Active substance	10.0 mg
Powdered lactose	70.0 mg
Corn starch	31.0 mg
Polyvinylpyrrolidone	8.0 mg
Magnesium stearate	1.0 mg
	120.0 mg

Method of preparation

A mixture of the active substance, lactose and corn starch is moistened with a 20% solution of polyvinyl pyrrolidone in water. The moist mass is granulated through a screen with a mesh width of 1.5 mm and then dried at 45°C. The dried granulate is rubbed through a screen with a mesh size of 1 mm and homogeneously mixed with magnesium stearate.

Weight of tablet: 120 mg

Punch: 7 mm diameter with dividing slot.

Example D

Coated tablets containing 5 mg of 4-[(1-(2-piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid

1 tablet core contains:

Active substance	5.0 mg
Secondary calcium phosphate	70.0 mg
Corn starch	50.0 mg
Polyvinylpyrrolidone	4.0 mg
Magnesium stearate	1.0 mg
	130.0 mg

Method of preparation

A mixture of active substance, calcium phosphate and corn starch is moistened with a 15% solution of polyvinylpyrrolidone in water. The moist mass is passed through a screen with a mesh size of 1 mm, then dried at 45°C and passed through the same screen again. After the specified amount of magnesium stearate has been added, tablet cores are compressed from the mixture.

Weight of core: 130 mg

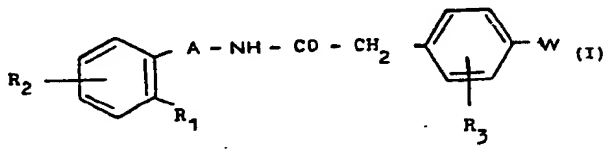
Punch: 7 mm in diameter.

A coating of sugar and talc is applied to the tablet cores thus produced in known manner. The finished coated tablets are polished with wax.

Weight of coated tablet: 180 mg

CLAIMS

1. Compounds of general formula I



[wherein

A represents a group of formula

[wherein R_4 represents an alkyl group containing 1 to 3 carbon atoms optionally substituted by an alkoxy group containing 1 to 3 carbon atoms or by a phenyl

group; an alkyl group containing 4 to 7 carbon atoms; an alkenyl group containing 3 to 5 carbon atoms; a cyano or alkyleneiminocarbonyl group containing 4 to 6 carbon atoms in the alkylene moiety; an aminocarbonyl group optionally mono- or disubstituted by alkyl or phenylalkyl groups each having 1 to 3 carbon atoms in the alkyl moiety (the substituents in the case of disubstitution being the same or different); an aryl group containing 6 or 10 carbon atoms optionally mono- or disubstituted by halogen atoms, or by alkyl, hydroxy, alkoxy, phenylalkoxy, alkylsulphenyl, alkylsulphinyl and/or alkylsulphonyl groups, the substituents in the case of disubstitution being the same or different and each alkyl moiety containing 1 to 3 carbon atoms; or a heteroaryl group containing 4, 5, 8 or 9 carbon atoms and 1 or 2 nitrogen atoms;

R_5 and R_6, which may be the same or different, represent hydrogen atoms or alkyl groups containing 1 to 5 carbon atoms, or R_5 and R_6 together with the carbon atom between them represent a phenylalkylidene group containing 1 to 4 carbon atoms in the alkylidene moiety];

R_1 represents an unbranched alkyleneimino group containing 4 to 9 carbon atoms optionally mono- or disubstituted by alkyl groups containing 1 to 3 carbon atoms (which in the case of disubstitution may be the same or different); or a dialkylamino group containing 1 to 5 carbon atoms in each alkyl component,

R_2 represents a hydrogen, fluorine, chlorine, bromine or iodine atom, or a hydroxy, trifluoromethyl, nitro, amino, piperidino, alkyl, alkoxy, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, phenylalkoxy, alkanoyloxy, alkanoylamino, alkylamino or dialkylamino group wherein the alkyl component may contain 1 to 3 carbon atoms in each case,

R_3 represents an alkyl group containing 1 to 3 carbon atoms or a hydrogen or halogen atom, and

W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 6 carbon atoms (wherein the alkyl component may optionally be substituted by a phenyl group and optionally, at any carbon atom except the α-carbon atom, by one or two hydroxy groups or by an alkoxy, alkanoyloxy, dialkylamino, alkyleneimino or pyridinecarbonyloxy group, each alkyl component containing 1 to 3 carbon atoms and the alkyleneimino group containing 4 to 6 carbon atoms); an alkenyloxycarbonyl group containing a total of 4 to 6 carbon atoms, an alkyl group containing 1 to 3 carbon atoms; or a hydroxymethyl, formyl, cyano, aminocarbonyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, 2,2-bis-(carboxy)-ethyl, alkoxycarbonyl-methyl, 2-alkoxycarbonyl-ethyl, 2-alkoxycarbonyl-ethenyl or 2,2-bis-(alkoxycarbonyl)-ethyl group (each alkoxy group containing from 1 to 3 carbon atoms)]

and tautomers thereof and optical enantiomers theeof and salts of the aforementioned compounds.

2. Salts of compounds of general formula I as defined in claim 1 and tautomers thereof, and optical enantiomers thereof, formed with hydrochloric, hydrobromic, sulphuric, phosphoric, lactic, citric, tartaric, succinic, maleic or fumaric acid or with sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, dethanolamine, triethanolamine or ethylenediamine.

3. Physiologically compatible salts of compounds of general formula I as defined in claim 1 and tautomers thereof, and optical enaniomers thereof.

4. Compounds as claimed in claim 1, wherein A represents a group of formula

wherein R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by an alkoxy group containing 1 to 3 carbon atoms or by a phenyl group; an n-propyl group; an alkyl group containing 4 to 6 carbon atoms; an alkenyl group containing 3 to 5 carbon atoms; a cyano or aminocarbonyl group; an aryl group containing 6 or 10 carbon atoms mono- or disubstituted by halogen atoms, or by alkyl, hydroxy, alkoxy, phenylalkoxy and/or alkylsulphenyl groups, whilst the substitutents may be the same or different and each alkyl component may contain from 1 to 3 carbon atoms; or a naphthyl, pyridyl, quinolyl or isoquinolyl group;

R_5 and R_6 together with the carbon atom between them represent an alkylidene group containing 3 to 9 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene moiety;

R_1 represents an unbranched alkyleneimino group containing 4 to 8 carbon atoms or a piperidino group mono- or disubstituted by alkyl groups each having 1 to 3 carbon atoms;

R_2 represents a hydrogen, fluorine, chlorine or bromine atom or a nitro, alkyl or alkoxy group each having 1 to 3 carbon atoms; or (if R_5 and R_6 are as hereinbefore defined or R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by an alkoxy group containing 1 to 3 carbon atoms or by a phenyl group, an n-propyl group, an alkyl group containing 4 to 6 carbon atoms, an alkenyl group containing 3 to 5 carbon atoms, or a nitrile or aminocarbonyl group) R_2 may also represent an iodine atom or a hydroxy or amino group;

R_3 represents a hydrogen or chlorine atom; and

W represents a methyl, hydroxymethyl, formyl, cyano, carboxy, carboxymethyl, 2-carboxy-ethyl or 2-carboxy-ethenyl group; an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms in which the alkyl component may be substituted at any carbon atom except the α-carbon atom by 1 or 2 hydroxy groups or by an alkoxy group containing 1 to 3 carbon atoms or by a pyridinecarbonyl-oxy group; or an alkoxycarbonyl-methyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group, wherein each alkoxy group may contain from 1 to 3 carbon atoms; and

4-[N-(6-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,

4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamic acid and C_{1-3} alkyl esters thereof;

3-[4-[(N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]phenyl]-propionic acid and C_{1-3} alkyl esters thereof,

4-[N-(4-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(3-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(2-(2-methyl-piperidino)-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[N-(2-(3-methyl-piperidino)-α-phenyl-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methylbenzaldehyde,
4-[(1-(4-fluoro-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[(1-(3-chloro-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof and
4-[(1-(3-methyl-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof, and tautomers and optical enantiomers of the above-named compounds and salts thereof.

5. Compounds as claimed in claim 1, wherein:
A represents a group of formula

wherein R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by a methoxy or phenyl group; an n-propyl, cyano or aminocarbonyl group; an alkyl group containing 4 to 6 carbon atoms, an alkenyl group containing 3 to 5 carbon atoms; a phenyl group substituted by a fluorine, chlorine or bromine atom or by a methyl, hydroxy, methoxy, benzyloxy or methylsulphenyl group; or a pyridyl group;
R_5 and R_6 together with the carbon atom between them represent an alkylidene group containing 3 to 9 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene moiety,
R_1 represents an unbranched alkyleneimino group containing 4 to 8 carbon atoms or a piperidino group mono- or disubstituted by methyl groups,
R_2 represents a hydrogen, fluorine, chlorine or bromine atom or a methyl or methoxy group; or, if R_5 and R_6 are as hereinbefore defined or R_4 represents an alkyl group containing 1 to 3 carbon atoms substituted by a methoxy or phenyl group, an n-propyl, nitrile or aminocarbonyl group, an alkyl group containing 4 to 6 carbon atoms or an alkenyl group containing 3 to 5 carbon atoms, R_2 may also represent an iodine atom or a hydroxy or amino group;
R_3 represents a hydrogen or chlorine atom; and
W represents a methyl, hydroxymethyl, formyl, cyano, carboxy, carboxy-methyl, 2-carboxy-ethyl or 2-carboxy-ethenyl group; an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms wherein the alkyl component may be substituted at any carbon atom except the α-carbon atom by one or two hydroxy groups, by an alkoxy group containing 1 to 3 carbon atoms or by a pyridinecarbonyloxy group; or an alkoxycarbonyl-methyl, 2-alkoxycarbonyl-ethyl or 2-alkoxycarbonyl-ethenyl group, wherein each alkoxy group may contain from 1 to 3 carbon atoms, and
4-[N-(6-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(α-phenyl-2-piperdino-benzyl)-aminocarbonylmethyl]-cinnamic acid and C_{1-3} alkyl esters thereof
3-[4-[(N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid and C_{1-3} alkyl esters thereof
4-[N-(4-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(3-chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof,
4-[N-(6-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[N-(4-methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[N-(2-(2-methyl-piperidino)-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[N-(2-(3-methyl-piperidino)-α-phenyl-benzyl)-aminocarbonylmethyl]-benzoic acid and the alkyl esters with 1 to 3 carbon atoms,
4-[N-(α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzaldehyde,
4-[(1-(4-fluoro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof
4-[(1-(3-chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof and
4-[(1-(3-methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof and tautomers and optical enantiomers of the above-named compounds and salts thereof.

6. Compounds as claimed in claim 5, wherein W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms in which the alkyl component may be substituted at any carbon atom except the α-carbon atom by one or two hydroxy groups.

7. Compounds as claimed in claim 5 wherein W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms.

8. Compounds as claimed in claim 1, wherein
A represents a group of formula

wherein R_4 represents an n-propyl group, an alkyl group containing 4 to 5 carbon atoms, a phenyl group substituted by a methyl group or by a fluorine or chlorine atom, or a pyridyl group;

R_5 and R_6 together with the carbon atom between them represent an alkylidene group containing 3 to 5 carbon atoms or a phenylakylidene group containing 1 to 3 carbon atoms in the alkylidene part;

R_1 represents a piperidino group optionally substituted by one or two methyl groups;

R_2 represents a hydrogen, fluorine or chlorine atom or a methyl or methoxy group;

R_3 represents a hydrogen atom; and

W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 4 carbon atoms.

9. Compounds as claimed in claim 8, wherein A represents a group of formula

wherein R_4 represents an n-propyl group or an alkyl group containing 4 to 5 carbon atoms and R_5 and R_6 together with the carbon atom between them represent an alkylidene group containing 3 to 5 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene part.

10. 4-[N-(6-Chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

11. 4-[N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-cinnamic acid and C_{1-3} alkyl esters thereof.

12. 3-[4-[(N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid and C_{1-3} alkyl esters thereof.

13. 4-[N-(4-Chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl-benzoic acid and C_{1-3} alkyl esters thereof.

14. 4-[N-(3-Chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

15. 4-[N-(6-Methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

16. 4-[N-(4-Methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

17. 4-[N-(2-(2-Methyl-piperidino)-α-phenyl-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

18. 4-[N-(2-(3-Methyl-piperidino)-α-phenyl-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

19. 4-[N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonylmethyl-benzaldehyde.

20. 4-[(1-(4-Fluoro-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

21. 4-[(1-(3-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

22. 4-[(1-(3-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

23. 4-[N-(6-Chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-benzoic acid and C_{1-3} alkyl esters thereof.

24. 4-[N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonyl-methyl]-cinnamic acid and C_{1-3} alkyl esters thereof.

25. 3-[4-[(N-(α-Phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-phenyl]-propionic acid and C_{1-3} alkyl esters thereof.

26. 4-[N-(6-Chloro-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof.

27. 4-[N-[α-(4-Fluoro-phenyl)-2-piperidino-benzyl]-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof.

28. 4-[N-(4-Methyl-α-phenyl-2-piperidino-benzyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof.

29. 4-[(1-(2-Piperidino-phenyl)-1-butyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof.

30. 4-[(1-(2-Piperidino-phenyl)-1 buten-1-yl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl. esters thereof.

31. 4-[(1-(2-Piperidino-phenyl)-1-pentyl)-aminocarbonylmethyl]-benzoic acid and C_{1-3} alkyl esters thereof.

32. Tautomers and optical enantiomers of compounds as claimed in any one of claims 10 to 31, and salts thereof.

33. Enantiomers and salts of compounds as claimed in any one of claims 23 to 31.

34. Compounds as claimed in claim 1 wherein A represents a group of formula

wherein R_4 represents an aryl group containing 6 or 10 carbon atoms mono- or di-substituted by halogen atoms, or by alkyl, hydroxy, alkoxy, phenylalkoxy, alkylsulphenyl, alkylsulphinyl and/or alkylsulphonyl groups, whilst the substituents in the case of disubstitution may be the same or different and each alkyl moiety may contain from 1 to 3 carbon atoms; or a heteroaryl group containing 4, 5, 8 or 9 carbon atoms and 1 or 2 nitrogen atoms;

R_1 represents an unbranched alkylenemino group containing 4 to 6 carbon atoms optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; an octahydroazocino, octahydro-1H-azonino or decahydroazecino group; or a dialkylamino group containing 1 to 5 carbon atoms in each alkyl component;

R_3 represents a hydrogen or halogen atom;

W represents a carboxy, formyl, hydroxymethyl, cyano, aminocarbonyl, 2-carboxyethenyl, 2-carboxyethyl, or 2,2-bis-(carboxy)-ethyl group, an

alkoxycarbonyl group containing a total of 2 to 5 carbon atoms, an ethenyl group monosubstituted at the 2-position by an alkoxycarbonyl group or an ethyl group mono- or di-substituted at the 2-position by alkoxycarbonyl groups (wherein each alkoxycarbonyl group may contain from 2 to 4 carbon atoms in total); and

R_2 represents a fluorine or bromine atom, a chlorine atom in the 3-, 4- or 6-position (relative to the substituent A), a nitro group or an alkyl or alkoxy group containing 1 to 3 carbon atoms; or (when either:

R_1 represents an unbranched alkyleneimino group substituted by one or two alkyl groups; an octahydroazocino, octahydro-1H-azonino or decahydroazecino group, or a dialkylamino group; and/or

R_4 represents an aryl group mono- or di-substituted by halogen atoms or by alkyl, hydroxy, alkoxy, phenylalkoxy, alkylsulfenyl, alkylsulfinyl and/or alkylsulfonyl groups; a naphthyl group; or a heteroaryl group containing 4, 5, 8 or 9 carbon atoms and 1 or 2 nitrogen atoms; and/or

W represents a hydroxymethyl, formyl, cyano, aminocarbonyl, 2-carboxyethenyl, 2-carboxyethyl or 2,2-bis-(carboxy)-ethyl group; an ethenyl group substituted at the 2-position by an alkoxycarbonyl group or an ethyl group mono- or di-substituted at the 2-position by alkoxycarbonyl groups; and/or

R_3 represents a halogen atom),

R_2 may also represent a hydrogen atom or a chlorine atom at the 5-position.

35. Compounds as claimed in claim 1, wherein A represents a group of formula

wherein R_4 represents an alkyl group containing 1 to 3 carbon atoms optionally substituted by an alkoxy group containing 1 to 3 carbon atoms or by a phenyl group; an alkyl group containing 4 to 6 carbon atoms; an alkenyl groups containing 3 to 5 carbon atoms; a cyano or alkyleneimino group containing 4 to 6 carbon atoms in the alkylene moiety; or an aminocarbonyl group optionally mono-disubstituted by alkyl or phenylalkyl groups each having 1 to 3 carbon atoms in the alkyl moiety;

R_5 and R_6, which may be the same or different, represent hydrogen atoms or alkyl groups containing 1 to 5 carbon atoms; or R_5 and R_6 together with the carbon atom between them represent a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene moiety;

R_1 represents an unbranched alkyleneimino group containing 4 to 8 carbon atoms or a piperidino group mono- or disubstituted by alkyl groups containing 1 to 3 carbon atoms;

R_2 represents a hydrogen, flourine, chlorine, bromine or iodine atom, an alkyl or alkoxy group wherein the alkyl component may contain 1 to 3 carbon atoms; or a hydroxy, nitro, amino or piperidino group;

R_3 represents a hydrogen, fluorine, chlorine or bromine atom; and

W represents a carboxy group or an alkoxycarbonyl group containing a total of 2 to 5 carbon atoms, or an alkyl group containing 1 to 3 carbon atoms.

36. Compounds as claimed in claim 1 as herein specifically described.

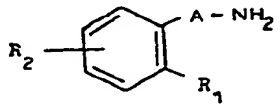
37. Compounds as claimed in claim 1 as herein specifically described in any of Examples 1 to 51.

38. Compounds as claimed in claim 34 as herein specifically described in any of Examples 1 to 14.

39. Compounds as claimed in claim 35 as herein specifically described as in any of Examples 22, 27, 38, 48 and 49.

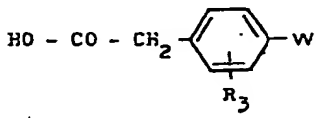
40. Compounds as claimed in any preceding claim for use in a method of treatment of diabetes mellitus and disorders of the intermediate metabolism or the cardiac circulatory system.

41. A process for the preparation of compounds as claimed in claim 1, which comprises reacting a compound of general formula II



(II)

(wherein A, R_1 and R_2 are defined as in claim 1 or, if A represents one of the vinylidene groups mentioned in claim 1, the tautomers thereof or a lithium or magnesium halide complex thereof) with a compound of general formula III



(III)

(wherein

R_3 is defined as in claim 1 and

W' has the meanings given for W in claim 1 or represents a carboxy group protected by a protecting group) or with a reactive derivative thereof optionally formed in the reaction mixture and, if necessary, subsequently cleaving any protecting group used.

42. A process as claimed in claim 41, wherein the reactive derivative of the compound of general formula III is an ester, thioester, halide, anhydride or imidazolide thereof.

43. A process as claimed in claim 41 or claim 42 wherein the subsequent cleaving of the protecting group of W', if present, is effected by hydrolysis, thermolysis or hydrogenolysis.

44. A process as claimed in claim 43 wherein the hydrolytic cleaving is effected in the presence of an acid or of a base.

45. A process as claimed in any of claims 41 to 44 wherein the reaction is effected in the presence of a solvent.

46. A process as claimed in any one of claims 41 to 45 wherein the reaction is effected in the presence of an acid-activating or dehydrating agent.

47. A process as claimed in any one of claims 41 to 45 wherein the reaction is effected in the presence of an amine-activating agent.

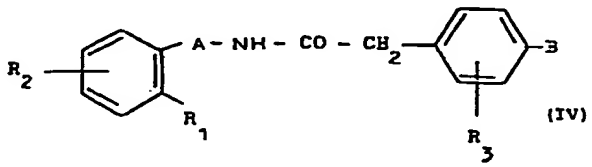
48. A process as claimed in any one of claims 41 to 47 wherein the reaction is effected in the presence of an inorganic or tertiary organic base.

49. A process as claimed in any one of claims 41 to 48 wherein water formed during the reaction is removed by azeotropic distillation or by the use of a drying agent.

50. A process as claimed in any one of claims 41 to 49 wherein the reaction is effected at temperatures of from −25 and 250°C.

51. A process as claimed in any one of claims 41 to 50 wherein a solvent is present and the reaction is effected at temperatures of from −10°C to the boiling temperature of the solvent.

52. A process for the preparation of compounds as claimed in claim 1 wherein W represents a carboxy, carboxymethyl, 2-carboxyethyl or 2-carboxyethenyl group, which comprises subjecting a compound of general formula IV



(IV)

(wherein R_1 to R_3 and A are as defined in claim 1 and B represents a group which can be converted into a carboxy, carboxymethyl, 2-carboxy-ethyl or 2-carboxy-ethenyl group by hydrolysis, thermolysis or hydrogenolysis) to hydrolysis, thermolysis or hydrogenolysis.

53. A process as claimed in claim 52 wherein the group B in the compound of general formula IV represents a functional derivative (if hydrolysis is desired), an ester (if thermolysis is desired) or an aralkyl ester (if hydrogenolysis is desired) of a carboxy, carboxymethyl, 2-carboxyethyl or 2-carboxyethenyl group.

54. A process as claimed in claim 53 wherein the functional derivative is an unsubstituted or substituted amide, nitrile, ester, thiolester, orthoester, imino ether, amidine or anhydride or a malonic ester-(1)-yl, tetrazolyl or optionally substituted 1,3-oxazol-2-yl or 1,3-oxazolin-2-yl group, the ester is a tertiary alkyl ester or the aralkyl ester is a benzyl ester.

55. A process as claimed in any one of claims 52 to 54, wherein the reaction is effected in the presence of a solvent.

56. A process as claimed in any one of claims 52 to 55, wherein the hydrolysis or thermolysis is effected in the presence of an acid or a base.

57. A process as claimed in any one of claims 52 to 55 wherein B in the compound of general formula IV represents a cyano or aminocarbonyl group and the reaction is effected using a nitrite in the presence of an acid.

58. A process as claimed in claim 57 wherein the nitrite is sodium nitrite and the acid used is sulphuric acid.

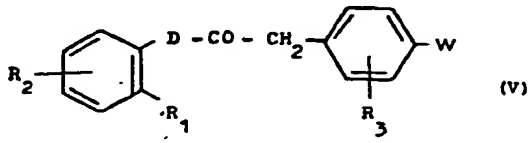
59. A process as claimed in any one of claims 52 to 58 wherein the reaction is effected at temperatures of from −10 to 120°C.

60. A process as claimed in any one of claims 52 to 59 wherein the reaction is effected at temperature of from ambient temperature to the boiling temperature of the reaction mixture.

61. A process for the preparation of compounds as claimed in claim 1 wherein A represents a group of formula

wherein R_4' has the meanings given for R_4 in claims 1 with the exception of an alkenyl group and a cyano group,

which comprises reduction of a compound of general formula V

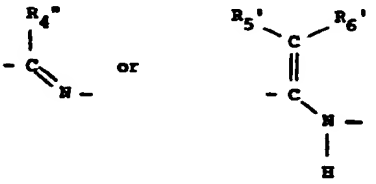


(V)

wherein

R_1 to R_3 and W are defined as in claim 1 and

D represents a group of formula



wherein R_4'' has the meanings given hereinbefore for R_4, with the exception of a cyano group and R_5' and R_6' together with the carbon atoms between them represent an alkylidene group containing 1 to 7 carbon atoms or a phenylalkylidene group containing 1 to 3 carbon atoms in the alkylidene moiety.

62. A process as claimed in claim 61, wherein the reduction is carried out with hydrogen in the presence of a hydrogenation catalyst.

63. A process as claimed in claim 62 wherein a hydrogen pressure of 1 to 5 bar is used.

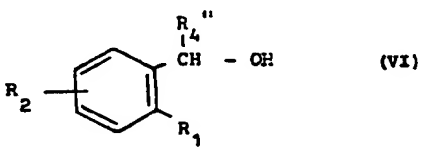
64. A process as claimed in any one of claims 61 to 63 wherein the reduction is carried out in a solvent.

65. A process as claimed in any one of claims 61 to 64 wherein the reduction is carried out at a temperature of from 0 to 100°C.

66. A process as claimed in claim 65, wherein the temperature is from 20 to 50°C.

67. A process for the preparation of compounds as claimed in claim 1 wherein A represents a group of formula

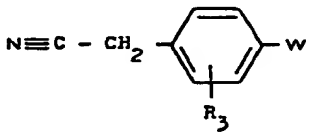
wherein R_4'' has the meanings given hereinbefore for R_4, with the exception of a cyano group; which comprises reacting a compound of general formula VI



(VI)

(wherein

R_4'' represents R_4 as defined in claim 1 with the exception of a cyano group and R_1 and R_2 are defined in claim 1) with a compound of general formula VII



(VII)

wherein R_3 and W are defined as in claim 1.

68. A process as claimed in claim 67, wherein the reaction is effected in the presence of a strong acid.

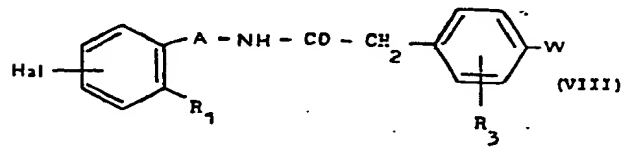
69. A process as claimed in claim 67 or claim 68, wherein the reaction is effected in the presence of sulphuric acid.

70. A process as claimed in any one of claims 67 to 69, wherein the reaction is effected in the presence of a solvent.

71. A process as claimed in any one of claims 67 to 70 wherein the reaction is effected at temperatures of from 0 to 150°C.

72. A process as claimed in claim 71 wherein the temperatures are from 20 to 100°C.

73. A process for the preparation of compounds as claimed in claim 1 wherein R_2 represents a hydrogen atom, which comprises dehalogenating a compound of general formula VIII



(VIII)

wherein R_1, R_3, A and W are as defined in claim 1 and Hal represents a fluorine, chlorine, bromine or iodine atom.

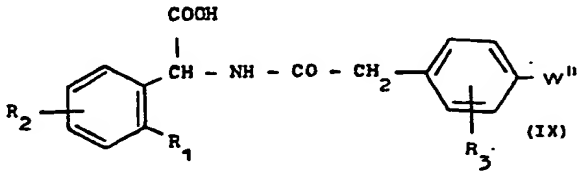
74. A process as claimed in claim 73 wherein the dehalogenation is effected with hydrogen in the presence of a hydrogenation catalyst.

75. A process as claimed in claim 73 or claim 74 wherein the dehalogenation is effected in a solvent.

76. A process as claimed in any one of claims 73 to 75, wherein the dehalogenation is effected at temperatures of between 0 to 100°C and under a hydrogen pressure of from 1 to 5 bar.

77. A process for the preparation of compounds as claimed in claim 1 wherein A represents a group of formula

wherein R_4 represents an alkyleneiminocarbonyl group containing 4 to 6 carbon atoms in the alkylene ring or an aminocarbonyl group optionally mono- or di-substituted by alkyl or phenylalkyl groups each having 1 to 3 carbon atoms in the alkyl moiety, which comprises reacting a compound of general formula IX



(IX)

(wherein R_1, R_2 and R_3 are as defined in claim 1 and W'' represents W as defined in claim 1 with the exception of a carboxy group) with an amine of general formula X

$$H - R_7 \qquad (X)$$

wherein

R_7 represents an alkyleneimino group containing 4 to 6 carbon atoms or an amino group optionally mono- or di-substituted by alkyl or phenylalkyl groups each containing 1 to 3 carbon atoms in the alkyl moiety.

78. A process as claimed in claim 77, wherein the reaction is effected in the presence of an acid-activating or dehydrating agent.

79. A process as claimed in claim 77 or claim 78, wherein the reaction is effected in the presence of an inorganic or tertiary organic base.

80. A process as claimed in any one of claims 77 to 79, wherein the reaction is effected in the presence of an amine-activating agent.

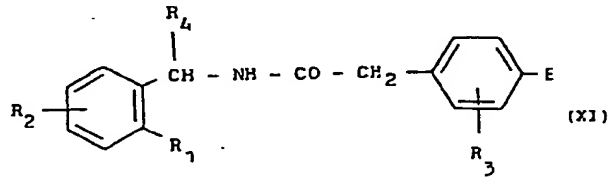
81. A process as claimed in any one of claims 77 to 80 wherein the reaction is effected in the presence of a solvent.

82. A process as claimed in any one of claims 77 to 81, wherein the reaction is effected at temperatures of from −25°C to 25°C.

83. A process as claimed in any one of claims 77 to 82 wherein the reaction is effected in the presence of a solvent and at temperatures of from −10°C to the boiling temperature of the solvent.

84. A process for the preparation of compounds as claimed in claim 1 wherein A represents a group of formula

wherein R_4 is as defined in claim 1 and W represents a carboxy group, which comprises oxidising a compound of general formula XI



(XI)

wherein

R_1 to R_4 are defined as in claim 1 and

E represents a group which can be converted into a carboxy group by oxidation.

85. A process as claimed in claim 84 wherein E represents a formyl group, an acetal of a formyl

group is subsequently converted by condensation and optional subsequent hydrolysis and/or decarboxylation into a corresponding compound of general formula I wherein W represents a 2 - alkoxycarbonyl - ethenyl or a 2 - carboxy - ethenyl group.

109. A process as claimed in any one of claims 41 to 108, wherein a compound of general formula I initially obtained wherein W represents a 2 - carboxy - ethenyl or 2 - alkoxycarbonyl - ethenyl group is subsequently converted by catalytic hydrogenation into a corresponding compound of general formula I wherein W represents a 2 - carboxyethyl or 2 - alkoxycarbonyl - ethyl group.

110. A process as claimed in any one of claims 41 to 109, wherein a compound of general formula I initially obtained wherein W represents an alkoxycarbonyl group substituted at any carbon atom except the α-carbon atom by a hydroxy group is subsequently converted by acylation by means of a pyridine-carboxylic acid into a corresponding (pyridine - carbonyloxyalkoxy) - carbonyl compound of general formula I.

111. A process as claimed in any one of claims 41 to 110, wherein a compound of general formula I initially obtained wherein W represents a hydroxymethyl group is, after being converted into a corresponding halomethyl compound, subsequently converted by reaction with a malonic acid diester into a corresponding compound of general formula I wherein W represents an ethyl group substituted by two alkoxycarbonyl groups.

112. A process as claimed in any one of claims 41 to 111, wherein a compound of general formula I initially obtained wherein W represents an ethyl group substituted by two alkoxycarbonyl groups is subsequently converted by hydrolysis into a corresponding compound of general formula I wherein W represents an ethyl group substituted by two carboxy groups.

113. A process as claimed in any one of claims 41 to 112, wherein a compound of general formula I initially obtained wherein W represents an ethyl group substituted by two alkoxycarbonyl groups is subsequently converted by hydrolysis and decarboxylation into a corresponding compound of general formula I wherein W represents a 2-carboxyethyl group.

114. A process as claimed in any one of claims 41 to 113, wherein a compound of general formula I initially obtained wherein R_2 represents a nitro group is subsequently converted by reduction into a corresponding compound of general formula I wherein R_2 represents an amino group.

115. A process as claimed in any one of claims 41 to 114, wherein a compound of general formula I initially obtained wherein R_2 represents an amino group is subsequently converted, via a corresponding diazonium salt, into a corresponding compound of general formula I wherein R_2 represents a hydrogen or halogen atom or a hydroxy, alkoxy or alkylsulphenyl group.

116. A process as claimed in any one of claims 41 to 115, wherein a compound of general formula I initially obtained wherein R_2 represents a hydroxy group is subsequently converted by alkylation into a corresponding compound of general formula I wherein R_2 represents an alkoxy group.

117. A process as claimed in any one of claims 41 to 116, wherein a compound of general formula I initially obtained wherein R_2 represents a benzyloxy group and/or R_4 represents an aryl group substituted by a benzyloxy group is subsequently converted by debenzylation into a corresponding compound of general formula I wherein R_2 represents a hydroxy group and/or R_4 represents an aryl group substituted by a hydroxy group.

118. A process as claimed in any one of claims 41 to 117, wherein a compound of general formula I initially obtained wherein R_4 represents an aminocarbonylgroup is subsequently converted by dehydration into a corresponding compound of general formula I wherein R_4 represents a cyano group.

119. A process as claimed in any one of claims 41 to 118 wherein a compound of general formula I initially obtained is subsequently resolved, by chromatography on a chiral phase, into the enantiomers thereof, if it contains a chiral centre.

120. A process as claimed in any one of claims 41 to 119, wherein a compound of general formula I or a tautomer or optical enantiomer thereof, initially obtained, is subsequently converted to a salt thereof, or a salt of a compound of general formula I or a tautomer or optical enantiomer thereof, initially obtained, is subsequently converted to a compound of general formula I or a tautomer or optical enantiomer thereof.

121. A process as claimed in any one of claims 41 to 120 for the preparation of compounds as claimed in claim 34.

122. A process as claimed in any one of claims 41 to 120 for the preparation of compounds as claimed in claim 35.

123. A process as claimed in any one of claims 41 to 122 substantially as herein described.

124. A process as claimed in any one of claims 41 to 123 substantially as herein described in any of Examples 1 to 51.

125. A process as claimed in claim 121 substantially as herein described in any of Examples 1 to 14.

126. A process as claimed in claim 122 substantially as herein described in any of Examples 22, 27, 38, 48 and 49.

127. Compounds of general formula I as defined in claim 1 and tautomers and optical enantiomers thereof, and salts of the afore-mentioned compounds, when prepared by a process as claimed in any one of claims 41 to 120, 123 and 124.

128. Compounds of general formula I as defined in claim 34 and tautomers and optical enantiomers thereof, and salts of the afore-mentioned compounds, when prepared by a process as claimed in claim 121 or claim 125.

129. Compounds of general formula I as defined in claim 35 and tautomers and optical enantiomers thereof, and salts of the afore-mentioned compounds, when prepared by a process as claimed in claim 122 or claim 126.

130. Pharmaceutical compositions comprising, an active ingredient, at least one compound of general formula I as defined in claim 1 or a tautomer

group, a hydroxymethyl group, an ether of a hydroxymethyl group, a substituted or unsubstituted acyl group or a malonic ester-(1)-yl group.

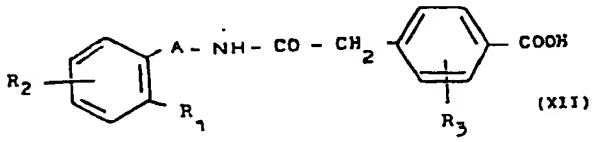
86. A process as claimed in claim 84 or claim 85 wherein the oxidising agent used is selected from: silver oxide/sodium hydroxide solution, manganese dioxide, hydrogen peroxide/sodium hydroxide solution, chromium trioxide/pyridine, pyridinium chlorochromate, bromine/sodium hydroxide solution, chlorine/sodium hydroxide solution, bromine/potassium hydroxide solution and chlorine/potassium hydroxide solution.

87. A process as claimed in any one of claims 84 to 86 wherein the oxidation is effected in the presence of a solvent.

88. A process as claimed in any one of claims 84 to 87 wherein the oxidation is effected at temperatures of from 0 to 100°C.

89. A process as claimed in claim 88 wherein the temperatures are from 20 to 50°C.

90. A process for the preparation of compounds as claimed in claim 1 wherein W represents an alkoxy-carbonyl group containing a total of 2 to 6 carbon atoms wherein the alkyl component may be substituted at any carbon atom except the α-carbon atom by one or two hydroxy groups or by an alkoxy group containing 1 to 3 carbon atoms, which comprises esterifying a carboxylic acid of general formula XII



(XII)

(wherein R_1 to R_3 and A are as defined in claim 1), or a reactive derivative thereof optionally prepared in the reaction mixture, with an alcohol of general formula XIII

$$HO — R_9 \qquad (XIII)$$

wherein

R_9 represents an alkyl group containing 1 to 5 carbon atoms which may be substituted at the β-carbon atom by one or two hydroxy groups or by an alkoxy group containing 1 to 3 carbon atoms.

91. A process as claimed in claim 90, wherein the reactive derivative of the compound of general formula XII, if present, is a halide, anhydride or imidazolide thereof.

92. A process as claimed in claim 90 or claim 91 wherein the esterification is effected in the presence of a solvent.

93. A process as claimed in claim 92 wherein the solvent is an excess of the alcohol of general formula XIII.

94. A process as claimed in any one of claims 90 to 93 wherein the esterification is effected in the presence of a reaction accelerator.

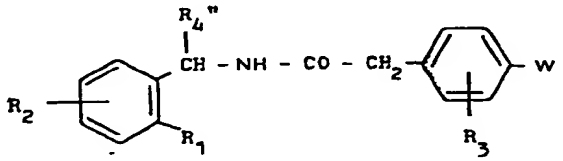
96. A process as claimed in any one of claims 90 to 95 wherein the esterification is effected in the presence of an inorganic or tertiary organic base.

97. A process as claimed in any one of claims 90 to 96 wherein the esterification is effected at temperatures of from −20 to 100°C.

98. A process as claimed in any one of claims 90 to 97, wherein the esterification is effected in the presence of a solvent and at temperatures of from −10°C to the boiling temperature of the solvent.

99. A process for the preparation of compounds as claimed in claim 1 wherein W represents an alkoxy-carbonyl, alkoxycarbonylmethyl, 2-alkoxy-carbonylethyl or 2-alkoxycarbonylethenyl group and A represents a group of formula

wherein R_4'' represents R_4 as hereinbefore defined with the exception of a cyano group, which comprises alcoholysing a compound of general formula XIV



(XIV)

wherein R_4'' represents R_4 as defined in claim 1 with the exception of a cyano group,

R_1 to R_3 are defined as in claim 1 and

W'' represents a cyano, cyanomethyl, 2-cyanoethyl or 2-cyanoethyenyl group.

100. A process as claimed in claim 99, wherein the alcoholysis is effected in the presence of an acid.

101. A process as caimed in claim 100 wherein the acid is hydrochloric or sulphuric acid.

102. A process as claimed in any one of claims 99 to 101, wherein the alcoholysis is effected in the presence of a solvent.

103. A process as claimed in claim 102 wherein the solvent is an excess of the alcohol used in the alcoholysis reaction.

104. A process as claimed in any one of claims 99 to 103, wherein the reaction is effected in the presence of a solvent and at temperatures of from 20°C to the boiling temperature of the solvent.

105. A process as claimed in any one of claims 99 to 104, wherein the reaction is effected at temperatures of between 50 and 100°C.

106. A process as claimed in any one of claims 41 to 105 wherein a compound of general formula I, initially obtained wherein W represents a carboxy or alkoxycarbonyl group is subsequently converted by reduction into a corresponding compound of general formula I wherein W represents a formyl or hydroxymethyl group.

107. A process as claimed in any one of claims 41 to 106, wherein a compound of general formula I, initially obtained wherein W represents a carboxy group is subsequently converted by conversion into a sulphonic acid hydrazide and subsequent disproportionation into a corresponding compound of general formual I wherein W represents a formyl group.

108. A process as claimed in any one of claims 41 to 107, wherein a compound of general formula I, intially obtained wherein W represents a formyl

or optical enantiomer thereof, or a physiologically compatible salt of these compounds, in association with at least one pharmaceutical carrier or excipient.

131. Compositions as claimed in claim 130 containing at least one additional active ingredient.

132. Compositions as claimed in claim 130 or claim 131 in a form suitable for oral or parenteral administration.

133. Compounds as claimed in any one of claims 130 to 132 in the form of tablets, coated tablets, capsules, powders or suspensions.

134. Compositions as claimed in any one of claims 130 to 133 in the form of dosage units.

135. Compositions as claimed in claim 130 wherein the active ingredient comprises a compound as claimed in claim 34 or claim 35.

136. Pharmaceutical compositions as claimed in claim 130 substantially as herein described.

137. Pharmaceutical compositions as claimed in claim 130 having hypoglycaemic activity.

138. Pharmaceutical compositions substantially as herein described in any one of Examples A to D.

139. A method of treatment of patients suffering from, or susceptible to, diabetes mellitus or disorders of the intermediate metabolism or the cardiac circulatory system, which comprises administering to the said patient an effective amount of a compound of general formula I as defined in claim 1 or a tautomer or a physiologically compatible salt thereof.

140. Each and every novel method, process, compound or composition herein disclosed.

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